THE SYNTHESIS OF HETEROCYCLIC BASES DERIVED FROM m-PHENANTHROLINE OF POSSIBLE ANTIMALARIAL ACTIVITY.

by

William Webster, B.Sc.

Thesis presented for the Degree of Ph.D.,

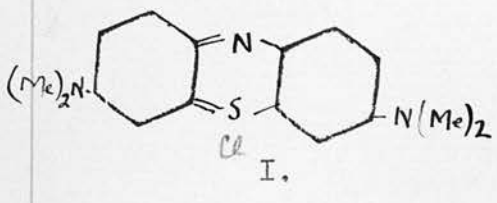
University of Edinburgh.

September 1941.

Contents.

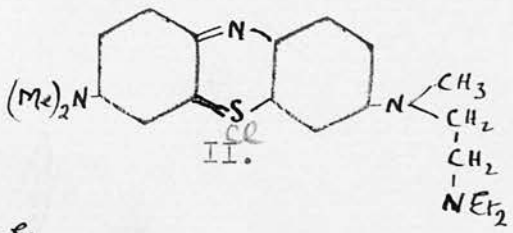
I. INTRODUCTION.

The search for a synthetic substitute for quinine was begun about eighty years ago, but most of the earlier work consisted of attempts to prepare compounds on the pattern of the quinine molecule and very little progress was made until a new method of approach to the problem was adopted. Thus, at Elberfeld, during the last war experiments were begun with methylene blue (I) which had been reported by Ehrlich as having some effect on the quartan parasite. Schulemann and his colleagues working on avian malaria found that this activity was increased when one of the methyl groups in methylene blue was replaced by a diethylamino-ethylamine group as in (II).

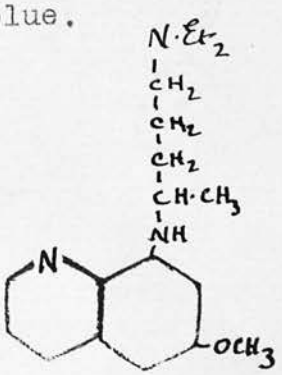


I.

Methylene blue.



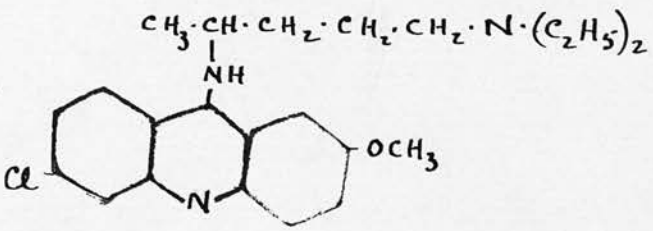
II.



III.
Plasmoquine.

It was then decided to introduce a similar modification into the quinoline nucleus and eventually from 8-aminoquinoline there was produced plasmoquine (III) or 8-(α-methyl- δ -diethylamino butylamino)-6-methoxy-quinoline. Plasmoquine has some activity against the benign, tertian and quartan parasites but it differs from quinine in being mainly gametocidal whereas the latter is schizonticidal.

With the object of getting rid of toxic properties said to be associated with the quinoline nucleus, Schulemann and his colleagues reverted to a triple ring system and by applying similar modifications to the acridine nucleus finally evolved atebrin (IV) or 2-chloro-5-(α-methyl- δ - diethylamino butyl amino)-7-methoxy acridine, which resembled quinine in being schizonticidal.

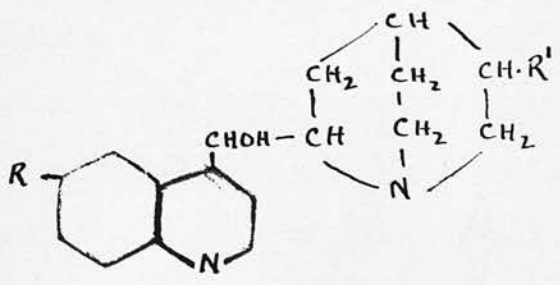


IV. Atebrin.

Since then a large amount of work has been done on the problem of the relationship between chemical/

chemical structure and antimalarial activity, and it may be useful to give a brief summary of the more significant results obtained in this field.

The existence of activity approaching that of quinine in compounds such as cinchonine (V) (R = H, R' = $CH{:}CH_2$) and dihydroquinine (V) (R = OCH_3, R' = $CH_2.CH_3$) shows that the methoxy and vinyl groups of quinine (V)(R = OCH_3, R' = $CH{:}CH_2$) can be considerably modified without loss of activity. On the other hand relatively small changes in the secondary alcohol (-CHOH-) group, e.g. chlorination (-CHCl-), acetylation (-CHOAc -) reduction ($-CH_2-$), oxidation (-CO-), etc., cause a disappearance of activity.



(V)

Quinine $\begin{cases} R = OCH_3 \\ R' = CH{:}CH_2 \end{cases}$

Oxidation of quinine under certain conditions yields/

yields the inactive acid quitenine (V) (R = OCH_3, R' = COOH) in which the vinyl group of quinine is replaced by a carboxylic group. Activity, however, is restored on esterification, and it was found by Goodson and coworkers (Biochem. J. 24, 874) that the activity of the ester produced increases with the molecular weight of the alcohol used for esterification, reaching a maximum at the butyl or amyl compound after which there is a decrease in activity.

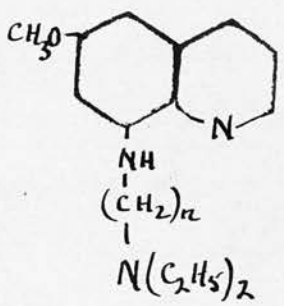
Variations in the activity of the members of another homologous series of compounds related to quinine was observed by Buttle and others (Biochem. J. 1938, 30, 41), who prepared a series of apoquinine ethers. Apoquinine, which can be obtained from quinine by the action of hydrochloric acid at high temperatures, is an isomer of cupreine (V) (R = OH, R' = $CH = CH_2$) but its internal structure is not yet fully known.

On testing these for therapeutic activity it was found that if the series was divided into members containing odd and even numbers of carbon atoms, there was a definite tendency in the two series so produced for the quinine ratio to rise to a maximum and then to fall off as the series is/

is ascended. The quinine ratio is the ratio of the increase in the time of appearance of parasites in drug treated birds to the increase in time of appearance in the birds treated with quinine.

Ether = $C_{19}H_{31}O_3N$ +	CH_3	C_2H_5	C_3H_7 (n)	C_4H_9 (n)	C_5H_{11} (n)	C_6H_{13} (n)	C_7H_{15} (n)	C_8H_{17} (n)	C_9H_{19} (n)	$C_{10}H_{21}$ (n)	$C_{11}H_{23}$ (n)	$C_{12}H_{25}$ (n)
i(even)	0.69		1.23		1.47		1.21		0.98		0.75	
i(odd)		1.18		1.10		1.72		1.6		1.18		0.58

A similar curious alternation in the parasiticidal activity of members of an homologous was noted by Magidson and co-workers (Terapeutichesky Arkhiv. 15, 693, 1937) in testing the activity of a series of 6-methoxy-8-dialkylamino-alkyl amino quinolines (VI) (cf. plasmoquine).



(VI)

The chemotherapeutic indices for different values of 'n' were found to be:

n	2	3	4	5	6	7	8	9	10	11
i		26		25		34		40		5
i	6		11		13					

Alternation of this type, however, is not always found in such tests with homologous series, for Magidson and Strukov, in the same paper, report that when the chain in position 8 in the above compound (VI) was kept constant at $-NH-(CH_2)_2.NEt_2$ and the group in position 6 varied from -OH to $-C_5H_{11}O$, there was a continuous but irregular fall in the chemotherapuetic indices from 1:13 to 0. Again, Magidson and Grigorowski (Chemico-Pharmaceutical Ind. (Russian) No.1, 1933) found that in 2-chloro-7-methoxy acridines substituted in position 5 by the chain $-NH-(CH_2)_nNEt_2$ where n = 2 to 6, , the chemotherapeutic indices began at 1:8, rose to 1:20 at n = 4 and fell to 1:6 and 1:5 at n = 5 and 6 respectively.

The discovery of plasmoquine led to a large number of attempts to synthesise antimalarials on/

on the pattern of the plasmoquine molecule. Among the earlier attempts was the production of 8-γ-amino propylamino-6-methoxy quinoline and the corresponding ethoxy compound (Baldwin, J.C.S. 1929, p. 2959; Tate and Vincent, Parasitology, 25, 411, 1933), both of which possessed curative action in avian malaria. Many homologues of plasmoquine have been prepared and tested, chiefly by Magidson and co-workers in Russia, and Fourneau and his colleagues in France. These compounds were mainly 6-methoxy-quinolines substituted in position 8 by different dialkylamino alkylamino chains. Of these may be mentioned Fourneau 710 or the methylene disalicylic acid salt of 6-methoxy-8-(γ-diethylamino-n-propylamino)-quinoline and Fourneau 574 which is 6-methoxy-8-(γ-dimethylamino-n-propylamino)-quinoline, both of which have activity of the same order as that of plasmoquine in human malaria.

As a result of their observations Fourneau and his co-workers believe that the presence of the methoxy group in position 6 of the quinoline nucleus is not absolutely essential for anti-malarial activity; but its replacement by higher alkoxy/

alkoxy groups seems to exert an unfavourable action. The complete omission of the methoxy group appears also to reduce the activity and this is also observed in the case of quinine and atebrin. On the other hand when it is replaced by an hydroxyl group, as in the commercial product known as "Certuna" (Kikuth, Klin. Woch. 1938, 17, 524) or "Cilional" (Chopra, Gupta and Sen, Ind. Med. Gazette, 1938, 73, 667) the antimalarial action remains marked. Certuna is described as a dialkylamino-butylamino-hydroxy quinoline and is said to possess high gametocidal activity.

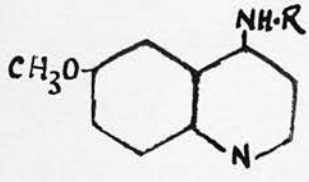
The most important of the derivatives of atebrin are the series of compounds prepared by Magidson and Grigorowsky mentioned above. The chief result of this work was the production of 2-chloro-7-methoxy-5-(γ-diethylamino-n-propyl-amino)-acridine which has a chemotherapeutic index equal to that of atebrin, and the corresponding δ-diethylamino-n-butylamino compound which has an even higher index.

Another recent development in quinoline and acridine antimalarials has recently been published by Knunianz and Benevolenskaya (J.Gen. Chem./

Chem. Russ. 1937, 7, 2930-33). By condensing chlorolupinan with 8-amino-6-methoxy quinoline they obtained 8-lupinyl-amino-6-methoxy quinoline, and by condensing 5:7-dichloro-3-methoxy-acridine with amino lupinan, 7-chloro-5-lupinylamino-3-methoxy acridine was obtained. Both of these compounds are claimed to be powerful antimalarials.

During the past four or five years a few antimalarially active compounds have been obtained which are not homologues or closely related derivatives of the three drugs quinine, plasmoquine and atebrin, and more attention is now being directed to the investigation of these newer compounds.

In 1937, a Russian paper by Magidson and Rubtzow (J. Gen. Chem. Russ, 1937, 1896-1908) described the preparation of some 4-dialkylamino-alkylamino-6-methoxy quinolines (VII) which were



(VII)

$$R = \begin{cases} -CH(CH_3).CH_2.CH_2.CH_2.N(C_2H_5)_2 \\ -CH_2.CHOH.CH_2.N(C_2H_5)_2 \\ -CH_2.CH_2.CH_2.CH_2.N(C_2H_5)_2 \end{cases}$$

found/

found to be active against bird malaria. An examination of the structure of these compounds shows that they may in a sense be regarded as intermediate between quinine (V) on the one hand and plasmoquine (III) on the other, but whether they are gametocidal or schizonticidal in action does not seem to have been so far reported.

Analogous compounds substituted in the 2-position instead of the 4- were prepared by the same authors but were found to be completely inactive, as also are the 4-substituted -6-methoxy-quinaldines. It is suggested that in the latter the methyl group is oxidised to a carboxylic group which destroys the activity.

All the synthetic antimalarials so far discussed have deviated considerably from quinine. They are all derivatives of quinoline or acridine, and if the latter is regarded as a quinoline nucleus substituted in the 2:3 position by a benzene ring, then, the possession of a quinoline nucleus is the only factor common to these compounds and quinine. The dialkylamino alkylamino side chain of the synthetic drugs contains two

nitrogen/

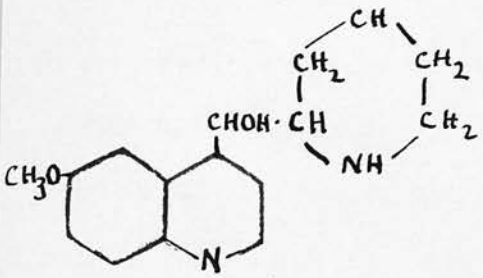
nitrogen atoms through one of which it is attached directly to the quinoline nucleus, while quinine possesses the characteristic quinuclidine structure containing one nitrogen atom, and attached to the quinoline nucleus through a carbinol group in such a way that the basic nitrogen atom of the side chain is separated from the nucleus by two carbon atoms.

Thus the essential difference in structure between the compounds discussed above and quinine lies in the nature of the side chains and the manner in which they are attached to the quinoline nucleus.

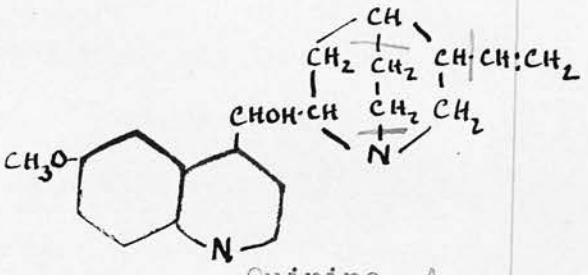
Within recent years King and his co-workers have endeavoured to synthesise a considerable number of compounds on the pattern of the quinine molecule and have succeeded in obtaining a number of such compounds which possess antimalarial activity. The chief result of this work was the preparation of 4-(6-methoxyquinolyl)-α-piperidyl carbinol (VIII)(Ainley and King, Proc. Roy. Soc. 1938, 125, 60) and dibutyl-,diamyl- and dihexyl-amino methyl-6-methoxy-4-quinolyl carbinols (IX).

(King/

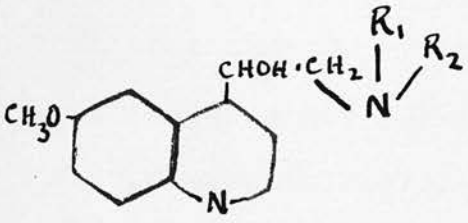
(King and Work, J.C.S. 1940, 1307), all of which possessed curative action in avian malaria.



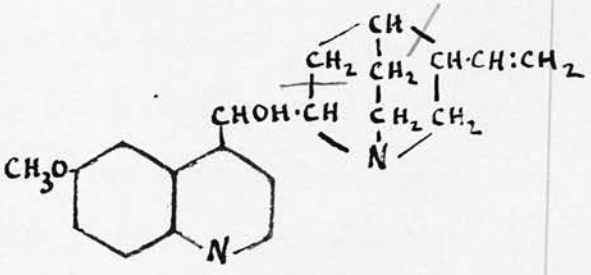
(VIII)



Quinine A



(IX)



B Quinine

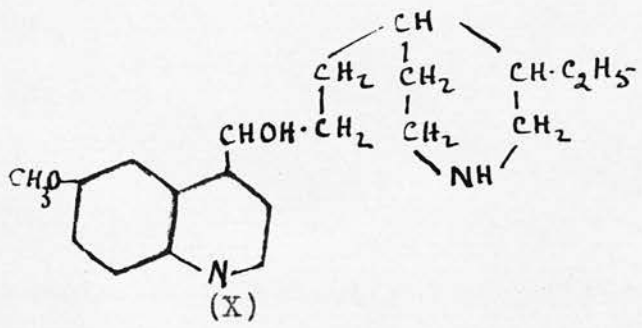
The intimate relationship between these compounds and quinine can be observed on comparing their structural formulae with that of quinine. Thus, 4-(6-methoxy quinolyl)-α-piperidyl carbinol can be represented as a quinine molecule cut at the points/

points indicated in diagram (A) and the dialkylamino-methyl-6-methoxy-4-quinolyl carbinols as a quinine molecule split at the two points shown in diagram (B).

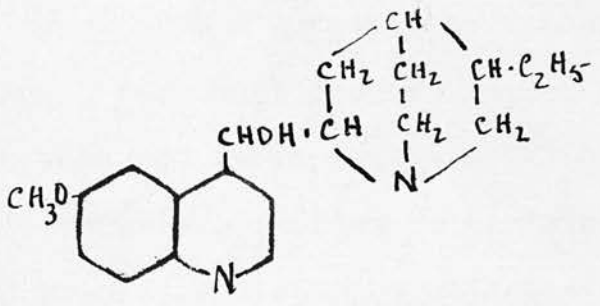
King and his co-workers also prepared the lower and higher homologues of compound (IX), a series of 1:2-carbinolamines similar to (IX) but containing naphthyl and 6-methoxy naphthyl groups in place of the 6-methoxy quinolyl group, and derivatives of both (VIII) and (IX) lacking the methoxy group. None of these compounds possessed antimalarial activity. These results indicate that in compounds related to quinine, antimalarial activity does not depend on the intact "quinnuclidine half" of the molecule, but on the other hand do suggest that the "quinoline half" is important. The importance of the "quinoline half" is further stressed by the results of Work (J.C.S. 1940, 1315) who prepared a wide variety of carbinolamines and polyamines of molecular weights of the same order as that of quinine but in which the quinoline nucleus was replaced by an aliphatic chain or other aromatic nuclei. None of these compounds were active/

active against malaria and so it seemed that in compounds such as (VII), (VIII) and (IX) the "quinoline half" is a potent factor in the production of antimalarial activity.

In compounds synthesised on the pattern of the quinine molecule it is probable that a further condition for antimalarial activity is that the quinoline nucleus should be separated from the nitrogen atom of the side chain by two carbon atoms as in quinine, for it is found that the d- and l-hydroquinicinols (X) which are γ -piperidine derivatives are inactive in spite of their close relationship to dihydroquinine (XI).



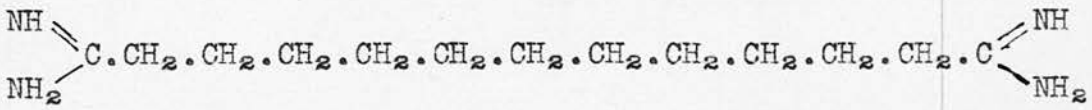
(X)



(XI)

There/

There seems to be one exception to the observation made above that all compounds possessing antimalarial activity contain a quinoline nucleus or a modified form of it. In 1937 King, Yorke and Lourie (Lancet 1937, 223, 1360) discovered that a series of long chain aliphatic compounds with terminal guanidine or amidine groupings possessed direct trypanocidal action, the optimal activity occurring when the chain possessed eleven methylene groups. Later it was found that undecamethylene-diamidine (XII) caused the disappearance of malarial parasites from the blood of birds, monkeys and man.



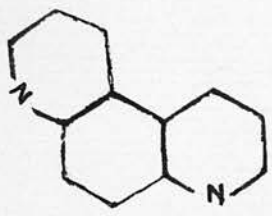
(XII)

The existence of activity in a compound of this type therefore opens up a new field of possibilities in the search for a curative substance.

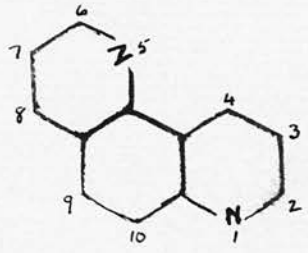
Apart from this isolated case, however, all the compounds of known antimalarial activity do contain either a quinoline or acridine nucleus and in the present research the object was the synthesis/

synthesis of compounds resembling plasmoquine and atebrin but containing a modified form of the quinoline nucleus, so that these compounds may be tested for antimalarial activity.

Recently Kermack and Weatherhead (J.C.S. 1940, 1184) published a paper describing the synthesis of various basic derivatives of p-phenanthroline or 5:6,3':2'pyrido quinoline (XIII).



(XIII)



(XIV)

The present research constitutes an extension of this work with a view to the synthesis of various di-alkylamino alkylamino derivatives of m-phenanthroline (XIV).

A number of derivatives of m-phenanthroline substituted in position 10 by dialkylamino alkylamino side chains are described in some recent patents/

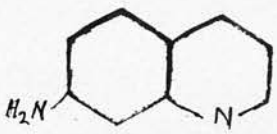
patents (C. 1936, II, 663; 1937, I, 663; 1937, I, 1478). These contain the basic side chain in the benzene ring, and bear some resemblance to plasmoquine, but whether or not they possess antimalarial activity does not seem to have been so far reported.

The compounds described in this work, however, differ from these in containing the side chain in one of the pyridine nuclei, in either the 2,4, 6 or 8 position.

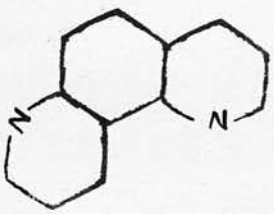
II. Nomenclature and Identification of Derivatives of m-Phenanthroline.

m-Phenanthroline (III) can be obtained by performing the Skraup synthesis on either m-phenylenediamine (I) (Skraup, Vortmann, M. 3, 571), or 7-amino quinoline (II)(Skraup, M.5, 532).

I.

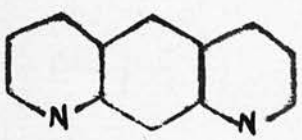


II.

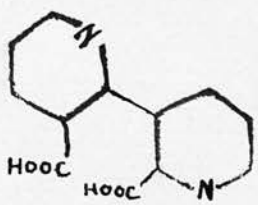


III.

Theoretically, the Skraup synthesis on m-phenylene diamine or 7-amino quinoline would produce a compound having either the angular structure (III) or the linear structure IV. It was shown by Skraup and Vortmann (loc. cit.) that m-phenanthroline actually possessed the angular structure, because on oxidation with potassium permanganate, it yielded 2:3'-dipyridyl-3:2'-dicarboxylic acid (V).



IV.

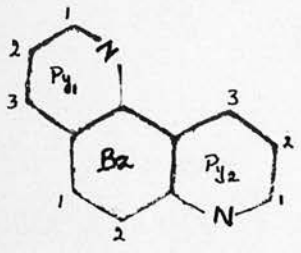


V.

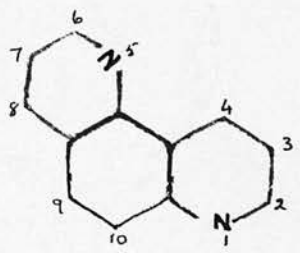
This/

This result is in agreement with many observations which suggest that, when ring closure can take place in either of two ways involving respectively an angular and a linear structure, the angular structure is invariably formed.

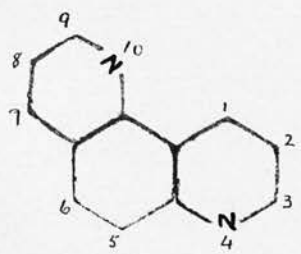
m-Phenanthroline may be regarded as a benzene ring condensed with two pyridine rings but it is to be noted that corresponding positions in the two pyridine rings are not equivalent, as they are in the case of o- and p-phenanthrolines. Consequently, on monosubstitution in one of the pyridine rings, two isomeric compounds are possible for each position in the pyridine nucleus. Thus, in numbering the various substitution positions in m-phenanthroline it is necessary to distinguish each of the two pyridine rings. In earlier work the various positions were numbered as in (VI) in which all three rings are identified as



VI



VII

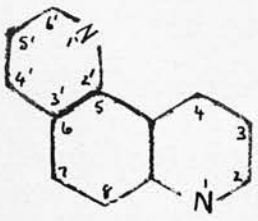


VIII

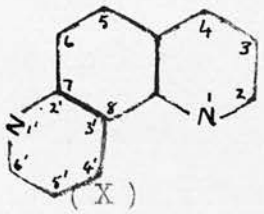
pyridine 1/

pyridine 1, benzene and pyridine 2 respectively. This cumbersome method was replaced by the systems shown in VII and VIII in which each substitution position is numbered separately, and which are also applicable to o- and p-phenanthrolines. To distinguish it from the latter m-phenanthroline is called 1:5-phenanthroline according to (VII) or 4:10-phenanthroline according to (VIII).

The phenanthroline structure however, can also be regarded as a quinoline nucleus condensed with a pyridine ring and so m-phenanthroline may be called 5:6,2':3'-pyrido quinoline (IX) or 7:8,2':3'-pyrido quinoline (X).



(IX)



(X)

The advantage of this method of nomenclature is not so obvious when dealing with m-phenanthroline itself, in which both structures (IX) and (X) are/

are identical, as when dealing with substituted m-phenanthrolines. With the latter, the use of this method makes it easier to distinguish the various possible isomers, the more so because the majority of these derivatives are obtained from substituted quinoline intermediates.

For this reason the pyrido quinoline nomenclature is used in the present work.

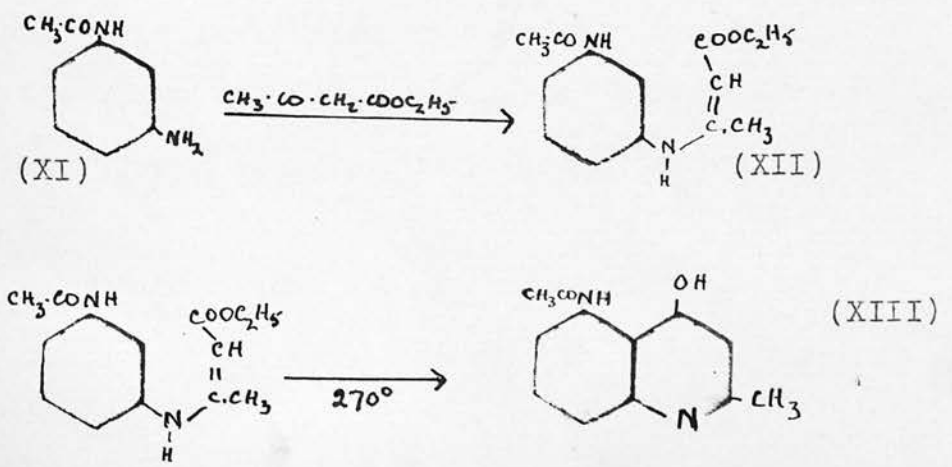
The object of this work was the preparation of 5:6- and 7:8-pyrido quinolines carrying a basic side chain in position 4 or position 2 of the quinoline nucleus. These were obtained by condensing the corresponding chloro derivatives with the appropriate bases, the former in turn being produced by the replacement of the hydroxyl group by chlorine in the corresponding hydroxy pyrido quinolines. It was found that the methyl derivatives of the latter were more easily accessible than the hydroxy pyrido quinolines themselves and consequently 3 of the 5 hydroxy pyrido quinolines prepared in this work are 2- or 4-methyl substituted derivatives.

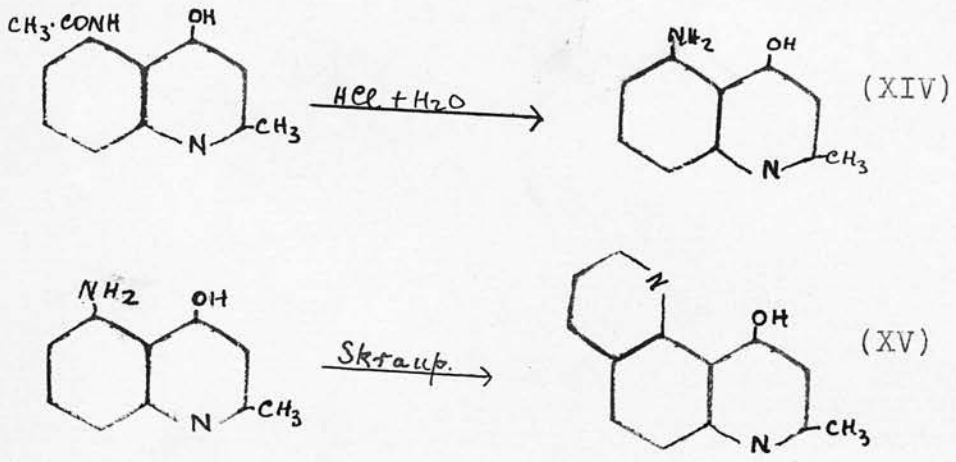
These hydroxy pyrido quinolines were obtained in practice by one or other of the two following methods. The first consists of preparing a 5- or 7-amino quinoline containing an hydroxy group in position 2 or 4 and subjecting it to the Skraup synthesis. The second of condensing 5- or 7-amino quinolines with aceto-acetic ester by Conrad and Limpach's method. These syntheses are dealt with in detail in the appropriate sections of the thesis, but to avoid confusion in the identification of the various pyrido quinoline derivatives a brief summary of the synthesis and identification of the hydroxy pyrido quinolines is given below.

(i) 2-Methyl-4-hydroxy-5:6,2':3'-pyrido quinoline

(see pp. 33-42)

This compound was synthesised according to the following scheme.

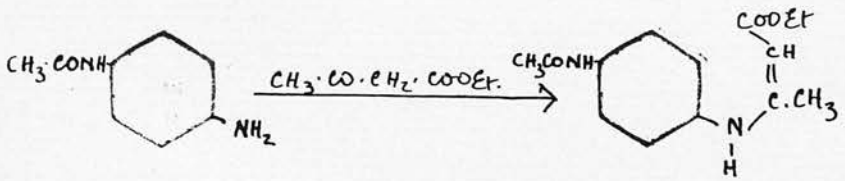


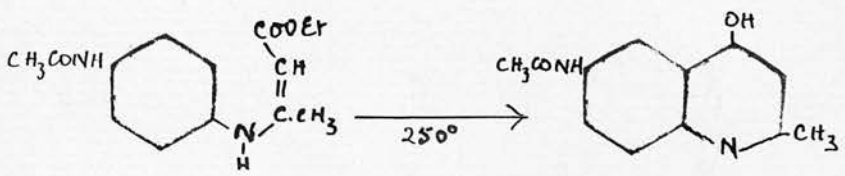


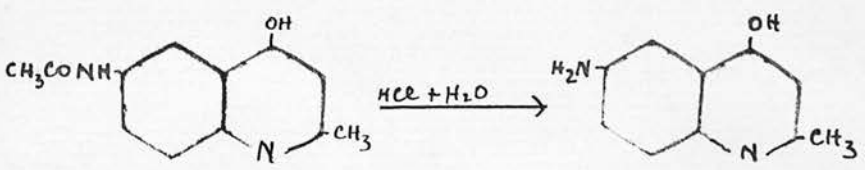
m-Amino acetanilide (XI) and aceto acetic ester were condensed to give ethyl-β-3-acetamido phenyl-amino crotonate (XII) which on ring closure in paraffin at 270° yielded 5-acetyl amino-4-hydroxy-2-methyl quinoline (XIII). The corresponding amino compound was obtained on hydrolysis and from it 2-methyl-4-hydroxy-5:6,2':3'-pyrido quinoline (XV) was obtained by the Skraup synthesis. This compound melted at 142° and on treatment with phosphorus oxychloride and phosphorus pentachloride yielded 2-methyl-4-chloro-5:6,2':3'-pyrido quinoline. m.p. 140°.

It is theoretically possible that on ring closure ethyl-β-3-acetamido phenylamino crotonate would yield 7-acetylamino-4-hydroxy-2-methyl quinoline (XVI). The latter on hydrolysis followed by the Skraup reaction would yield, if we ignore the/

In an earlier paper (J.C.S. 1939, 563) these authors described a convenient method of preparing 6-amino-4-hydroxy-2-methyl quinoline from p-amino acetanilide by condensing the latter, by Conrad and Limpach's method, with acetoacetic ester, cyclising the product in paraffin at 250° and removing the acetyl group by hydrolysis. This is shown in the following scheme:

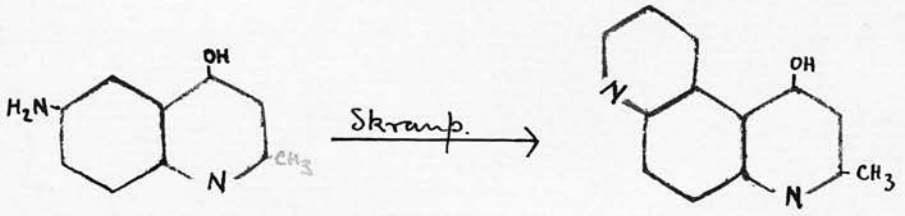


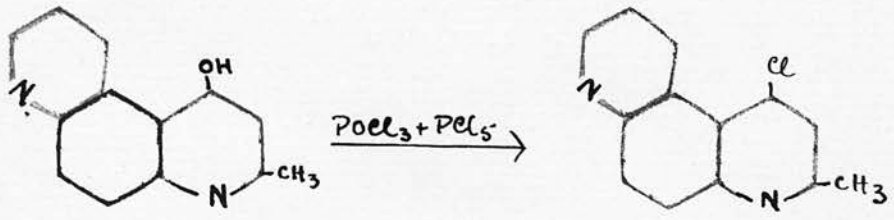


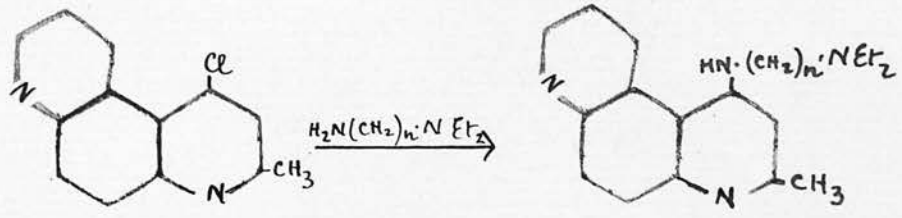


In/

A recent paper (J.C.S. 1940, 1164) by Kermack and Weatherhead described the synthesis of 4-dialkylamino-alkylamino-2-methyl-5:6,3':2'-pyrido quinolines from 2-methyl-4-hydroxy-6-amino quinoline according to the following scheme of synthesis:



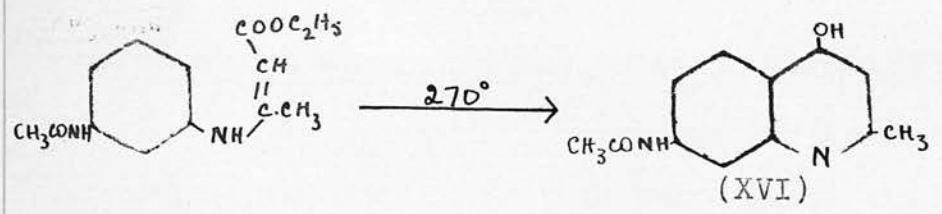




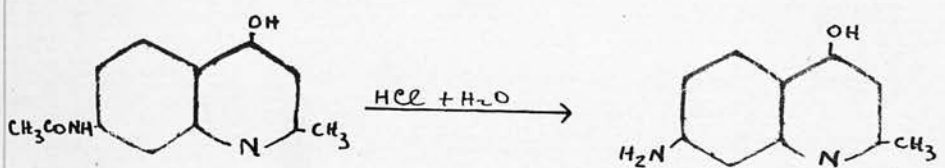
In/

III. The Synthesis of 4-dialkylamino alkylamino-2-methyl-5:6,2':3'-pyrido quinolines.

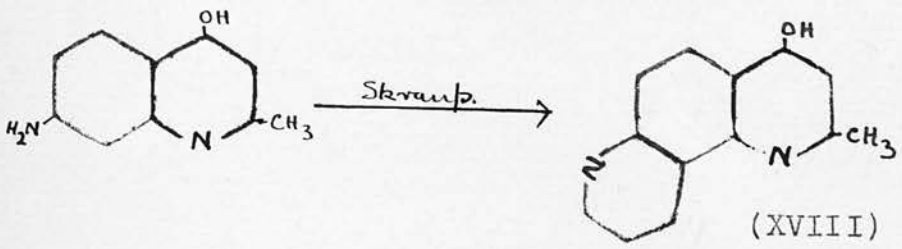
the possibility of the alternative linear structure, 2-methyl-4-hydroxy-7:8,2':3-pyrido quinoline (XVIII), as shown in the following scheme.



(XVI)



(XVII)



(XVIII)

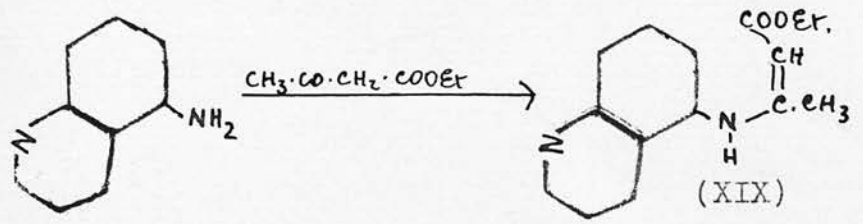
2-Methyl-4-hydroxy-7:8,2':3'-pyrido quinoline had already been prepared by a different method (see (ii) below); it does not melt below 345° and is an entirely different compound from that obtained/

obtained by us by this method. Thus the compound obtained on cyclising ethyl-β-3-acetamido phenyl-amino crotonate must be 5-acetylamino-4-hydroxy-2-methyl quinoline.

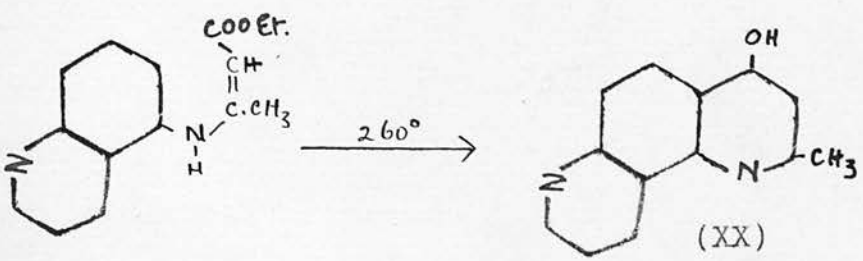
(ii) 2-Methyl-4-hydroxy-7:8,2':3'-pyrido quinoline

(see pp. 43-50)

The preparation of this compound is described by Hughes and Lions (J. Proc. Roy. Soc. New South Wales, 1937-38, 71, 472), who obtained it by condensing 5-aminoquinoline with aceto acetic ester by Conrad and Limpach's method as shown by the following scheme.



(XIX)



(XX)

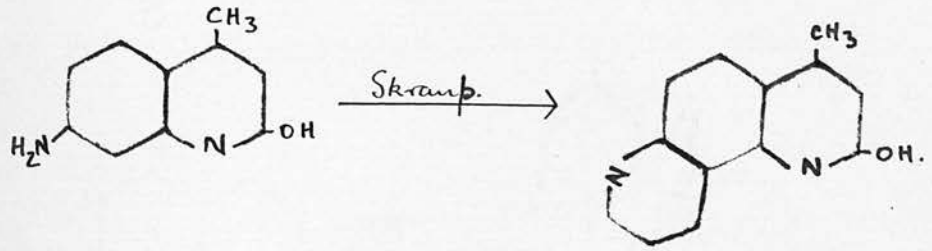
On/

On repeating this synthesis we obtained 2-methyl-4-hydroxy-7:8,2':3'-pyrido quinoline (XX) which on heating began to sublime with decomposition about 300° and melted completely at 395°. On treatment with phosphorus pentachloride and phosphorus oxychloride 2-methyl-4-chloro-7:8,2':3'-pyrido quinoline, m.p. 190°, was obtained.

(iii) 2-Hydroxy-4-methyl-7:8,2':3'-pyrido quinoline

(see pp. 51-57)

A convenient starting material for the synthesis of this compound was found in 7-amino-4-methyl-2-hydroxy quinoline which had previously been obtained by Besthorn and Byvanck (Ber. 1898, 31, 796) by condensing m-phenylenediamine with aceto acetic ester.

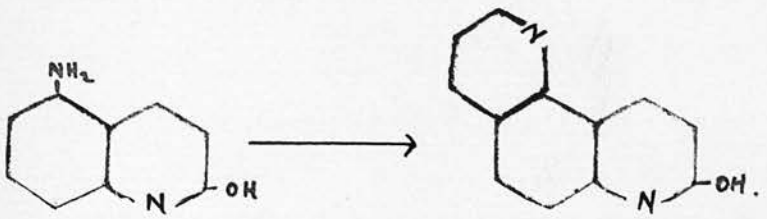


(XXI) (XXII)

This compound was subjected to the Skraup synthesis when, the possibility of a linear structure being ignored, 2-hydroxy-4-methyl-7:8,2':3'-pyrido quinoline (XXII) was obtained. It began to sublime with decomposition about 305° and melted completely at 315°. On replacing the hydroxyl group by chlorine with phosphorus oxychloride and phosphorus pentachloride it yielded 2-chloro-4-methyl-7:8,2':3'-pyrido quinoline, m.p. 161°.

(iv) 2-Hydroxy-5:6,2':3'-pyrido quinoline and 2-Hydroxy-7:8,2':3' pyrido quinoline (See pp. 58-74)

2-Hydroxy-5:6,2':3'-pyrido quinoline (XXIV) was obtained by carrying out the Skraup synthesis on 5-amino-2-hydroxy quinoline (XXIII) as shown in the scheme below. The latter

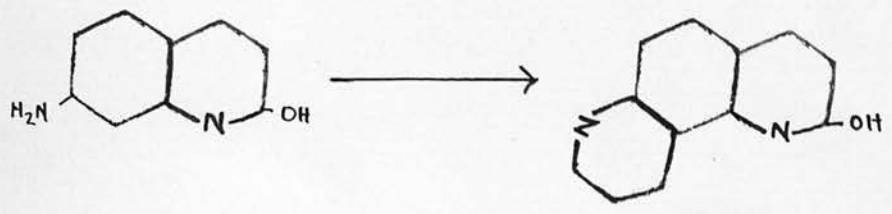


(XXIII) (XXIV)

compound/

compound was prepared by the method of Capps and Hamilton (J.A.C.S. 1938, 2104); it consists of oxidising 5-nitroquinoline to 5-nitro-2-hydroxy quinoline with sodium hypochlorite as oxidising agent and subsequently reducing it to the corresponding amino compound. 2-Hydroxy-5:6,2':3'-pyrido quinoline began to sublime with decomposition about 290° and melted at 312-313°. It reacted with phosphorus oxychloride and phosphorus pentachloride to yield 2-chloro-5:6,2':3'-pyrido quinoline, m.p. 145-146°.

Capps and Hamilton, in the same paper, describe the preparation of 7-amino-2-hydroxy quinoline (XXV) by a similar series of reactions on 7-nitro quinoline. The preparation of this compound was repeated by us and the product was submitted to the Skraup synthesis when, if we again ignore the possibility of a linear structure being formed, 2-hydroxy-7:8,2':3'-pyrido quinoline (XXVI) was obtained. This compound on heating



(XXV) (XXVI)

began/

began to change in appearance about 275° and on further heating a small amount of sublimation took place. It melted completely at 290°. On treatment with phosphorus oxychloride and phosphorus pentachloride it yielded 2-chloro-7:8, 2':3'-pyrido quinoline, m.p. 160°

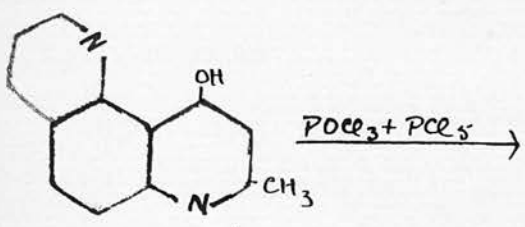
In the German patent D.R.P. 654,444 (C., 1938, I, 2023) there is described the preparation of a compound which melts at 151° and is given the formula 2-chloro-m-phenanthroline (i.e. XXV) This compound was obtained by treating m-phenanthroline with dimethyl sulphate to yield N-methyl-m-phenanthrolinium methyl sulphate. The latter was oxidised with potassium ferricyanide to N-methyl-m-phenanthrolone which on treatment with phosphorus pentachloride yielded 2-chloro-m-phenanthroline. This scheme of synthesis, however, can follow two routes, depending on which of the nitrogen atoms of m-phenanthroline is involved, to yield either 2-chloro-5:6,2':3'-pyrido quinoline or 2-chloro-7:8,2':3'-pyrido quinoline (see pp.62-65). On repeating this synthesis there was obtained a chloro pyrido quinoline/

quinoline which after recrystallising once from alcohol melted at 138°. The yield was too poor to permit of further purification but when mixed with 2-chloro-5:6,2':3'-pyrido quinoline it melted at 138-142°. When mixed with 2-chloro-7:8,2':3'-pyrido quinoline it melted at 119-125°. Thus the compound described in the patent must be 2-chloro-5:6,2':3'-pyrido quinoline.

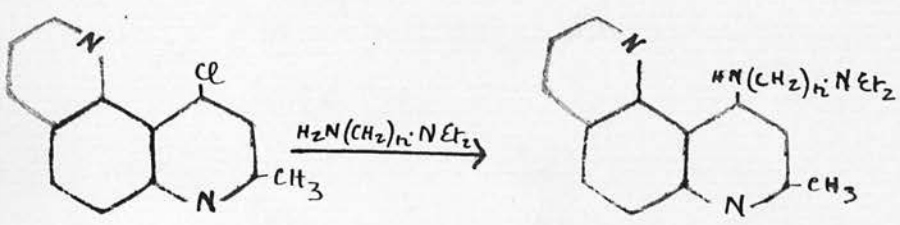
In the present work it was proposed to prepare pyrido quinoline derivatives,by a similar scheme of synthesis, from m-amino-acetanilide as starting material. With the latter, however, it is obvious that cyclisation can take place in either of two possible ways, to yield either 5-acetylamino-4-hydroxy-2-methyl quinoline or 7-acetyl-amino-4-hydroxy-2-methyl quinoline. On hydrolysis and subjection to the Skraup synthesis these compounds would yield 2-methyl-4-hydroxy 5:6,2':3'-pyrido quinoline and 2-methyl-4-hydroxy-7-8',2':3'-pyrido quinoline respectively. The evidence deduced in Section II (pp. 25-27) shows that the hydroxy pyrido quinoline formed corresponds in fact to the first of these two possibilities; the other having been previously synthesised by a different method.

It is of interest to note that when m-phenylenediamine is condensed with ethylaceto-acetate as described in Section (V) it yields 7-amino-2-hydroxy-4-methyl quinoline and not the 5-amino derivative. When the Skraup reaction is/

is carried out on m-nitraniline (cf. Section both 5- and 7-nitro quinolines are formed, the former preponderating. Similarly the Skraup reaction on m-chloro-aniline (La Coste, Ber. 18, 2940, 1885) yields both 5- and 7-chloro quinolines. It would seem therefore that cyclisation with meta substituted derivatives can take place in both ways and that minor influences may determine in what proportions the two products will be obtained. From 2-methyl-4-hydroxy-5:6,2':3'-pyrido-quinoline (I) obtained as above the required bases were prepared according to the scheme shown below.



(I) (II)



(III)

The/

The synthesis of ethyl-β-3-acetamido phenylamino crotonate (Section II, formula XII) from m-amino acetanilide and acetoacetic ester had already been performed by Backeberg (J.C.S. 1935, II, 1568) who obtained it by heating equimolecular quantities of the reactants on the water bath for half an hour and then leaving the mixture to stand for several days over phosphoric oxide. In our experiments a trace of hydrochloric acid was used as catalyst (Coffey, Thomson and Wilson, J.C.S. 1936, I, 856). By this modification, the condensation was effected by heating on the water bath for less than half an hour and allowing to cool when the product gradually solidified to a hard crystalline mass.

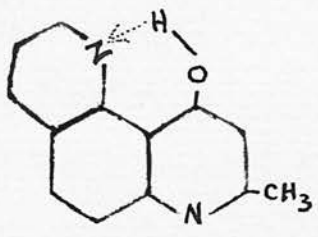
Backeberg (loc. cit.) was unable to convert this compound into a quinoline derivative. We found, however, that on adding it to medicinal paraffin at 270°, ring closure did take place to yield 5-acetylamino-4-hydroxy-2-methyl quinoline. (Section II, formula XIII). The latter compound however did not separate from the paraffin as a crystalline derivative except in very small quantity/

quantity, but was chiefly obtained as a sticky brown mass on the bottom of the flask from which it was extracted with boiling water. On re-crystallisation from hot water it was obtained as pale yellow needles, m.p. 236°. In this way 5-acetylamino-4-hydroxy-2-methyl quinoline was obtained in about 30% yield. This compound was easily hydrolysed by boiling with aqueous hydrochloric acid, when 5-amino-4-hydroxy-2-methyl quinoline (Section II, formula XIV) was obtained.

This compound when subjected to the Skraup synthesis yielded 2-methyl-4-hydroxy-5:6,2':3'-pyrido quinoline (I), m.p. 142°. The comparatively low m.p. of this compound is one feature which distinguishes it from the other hydroxy-pyrido quinolines described in this work. The latter all melted at various temperatures above 290° and moreover began to sublime at temperatures a few degrees below their melting points. In other properties, however, such as solubility in organic solvents and in acids and alkalis this compound bore a strong resemblance to the other hydroxy-pyrido quinolines.

A possible explanation of this fact may be found/

found in the assumption that in 2-methyl-4-hydroxy-5:6,2':3'-pyrido quinoline a chelate ring is formed involving a coordinate hydrogen bond between the hydrogen of the hydroxyl group and the adjacent nitrogen atom in the pyridine ring. This is shown in formula (IV) where the coordinate hydrogen bond is represented by (⋯▷).



(IV)

It will be observed that of all the hydroxy pyrido quinolines described in this work, the above is the only one in which the formation of such a chelate ring is possible. Owing to the weakness of the hydrogen bond, the existence of a chelate ring in a compound does not interfere with its chemical reactivity. In this case the effect of this chelation might be to stabilise the compound as the hydroxyl derivative as distinguished from the isomeric keto form (4-keto-1:4 dihydro-5:6,2':3'-pyrido/

pyrido quinoline), in which case the melting point might be expected to approach that of such compounds as 8-hydroxy 5:6,2':3'-pyrido quinoline, m.p. 158°, which presumably exist as true hydroxyl derivatives, and so to be abnormally low.

On heating 2-methyl-4-hydroxy-5:6,2':3-pyrido quinoline with redistilled phosphorus oxychloride and phosphorus pentachloride, the hydroxyl group was readily replaced by chlorine to yield 2-methyl-4-chloro-5:6,2':3'-pyrido quinoline (II), m.p. 140°.

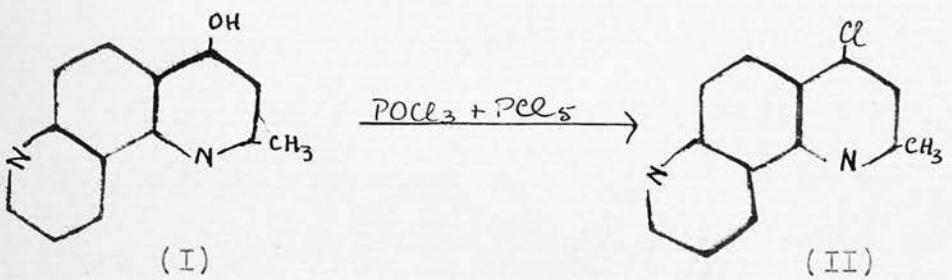
To complete the synthesis this chloro derivative was condensed with β-diethylamino ethylamine and α-methyl- δ -diethylamino-butylamine to yield the corresponding bases. Thus 2-methyl-4-β-diethylamino ethylamino 5:6,2':3'-pyrido quinoline was produced by heating at 150° for 6 hours and using a trace of copper bronze as catalyst. This base proved to be a heavy brown oil which did not crystallise and did not give a crystalline hydrobromide. It was conveniently isolated and purified as the dipicrate, m.p. 237°.

2-Methyl-4-(α-methyl- δ -diethylamino butylamino)-5:6,2':3' pyrido quinoline was obtained in a similar way by heating at 200° for 8 hours. It

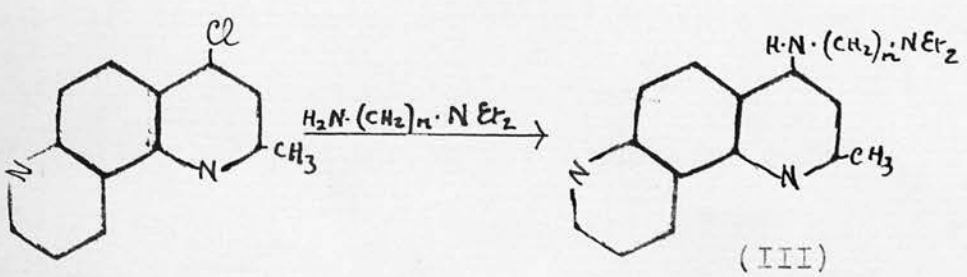
was found to be a heavy brown oil which did not crystallise and did not give a hydrobromide salt but was isolated as the dipicrate, m.p. 195°.

IV. The Synthesis of 4-dialkylamino-alkylamino-2-methyl-7:8,2':3'-pyridoquinolines.

The preparation of 2-methyl-4-hydroxy-7:8,2':3'-pyrido quinoline had already been described by Hazlewood, Hughes and Lions (J. Proc. Roy. Soc. New South Wales, 1937-38, 71, 472). They prepared it by condensing 5-amino quinoline with acetoacetic ester, by Conrad and Limpach's method, and cyclising the product in paraffin at 270°, as shown in the scheme of synthesis in Section II (p.27). This synthesis was repeated by us, and from the 2-methyl-4-hydroxy-7:8,2':3'-pyrido-quinoline (I) so obtained, the required bases were produced according to the following scheme.



(I) (II)



(III)

The 5-amino quinoline, required as starting material in this synthesis, was obtained by the reduction of 5-nitro-quinoline which in turn was prepared either by the nitration of quinoline sulphate or by the Skraup synthesis on m-nitraniline. By the first method a mixture of equal quantities of 5- and 8-nitroquinolines is obtained in about 80% yields, while the second method yields a mixture of 5- and 7-nitroquinolines in which the proportion of the 5-isomer to the 7- is approximately 4 to 1, in a total yield of 60% of theory.

The nitration of quinoline sulphate was carried out according to the method of Claus and Setzer (J. pr. [2] , 53, 390) using a mixture of fuming sulphuric and fuming nitric acids as nitrating agent. These authors used sulphuric acid containing 40% sulphuric anhydride while in our experiments the sulphuric acid used contained only 10% sulphuric anhydride. It was found, however, that the employment of this weaker acid did not seem to affect the yield of the nitrated products. The 5- and 8-nitroquinolines were separated from the resultant mixture by the method originally described/

described by Dufton (J.C.S. 61, 783) in which use is made of the insolubility of the nitrate of 5-nitroquinoline in dilute nitric acid.

The Skraup synthesis on m-nitraniline is generally used for obtaining 7-nitroquinoline rather than 5-nitroquinoline and in most earlier work it was supposed that 7-nitroquinoline and m-phenanthroline were the sole products of the reaction. It was shown by Decker (J.pr. [2], 63, 573) however, that 5-nitroquinoline was also obtained in this reaction and that its properties agreed with the description which many authors had ascribed to m-phenanthroline. In our experiments, in which arsenic acid was used as oxidising agent, we were unable to isolate any m-phenanthroline from the reaction. It seems that the production of m-phenanthroline depends on the type of oxidising agent used, as La Coste (Ber. 16, 675) using nitrobenzene appears to have obtained only m-phenanthroline as reaction product.

The first part of the synthesis was carried out as described by Knueppel (Ber. 29, 703, 1896). A mixture of arsenic acid, glycerine, sulphuric acid and m-nitraniline was boiled gently for about 12 hours/

hours, poured into water and the reaction product precipitated in the usual way with caustic soda. After filtering off and drying, it was extracted with ether, when a mixture of 5- and 7-nitroquinolines was obtained.

To separate the two isomers, use was made of the comparative insolubility of 7-nitroquinoline in cold petroleum ether, as described by Kochanska and Bobranski (Ber. 69, 1909, 1936), while the 5-nitroquinoline was purified further by recrystallising as the nitrate from dilute nitric acid.

The reduction of 5-nitroquinoline to 5-aminoquinoline was carried out in two different ways. In the first, the reduction method used was that of West (J.C.S. 1925, I, 494) in which the reducing agent is iron filings and hydrochloric acid in methylated spirits. The amine separated as the hydrochloride from which the free base was obtained by dissolving in water, making strongly alkaline and extracting with ether. It was purified by distilling in vacuum.

The second method of reduction was by the use of hydrogen with Raney nickel as catalyst. A recent paper by Albert and Ritchie (J. Proc. Roy. Soc. New South Wales, 74, 74-81, 1940) described the/

the effective use of this catalyst in reductions with hydrogen at ordinary temperatures and pressures and with very simple apparatus. The method consists of shaking an alcoholic solution or suspension of the nitro compound, in the presence of Raney nickel with a measured volume of hydrogen contained at the pressure of a few inches of water. With 5-nitroquinoline this method proved to be very effective; hydrogen was absorbed at the rate of about 50 c.c. per minute and when the absorption had ceased an almost theoretical yield of 5-nitroquinoline was obtained by filtering off the catalyst and distilling the alcoholic solution down to dryness.

The condensation of 5-aminoquinoline with acetoacetic ester and the ring closure of the product was carried out as described by Hazlewood, Hughes and Lions (loc. cit.). 2-Methyl-4-hydroxy 7:8,2':3'-pyridoquinoline was thus obtained in about 30% yields. These authors found that this compound appeared to alter slightly at 300° but did not melt below 345°. This fact was confirmed by our work in which it was found that the compound began to sublime with decomposition about 300° and on continued heating finally melted about 395°.

On/

On heating this compound with phosphorus oxychloride and phosphorus pentachloride, replacement of the hydroxy group by chlorine took place, to yield 2-methyl-4-chloro-7:8'2':3'-pyridoquinoline which melted at 190°.

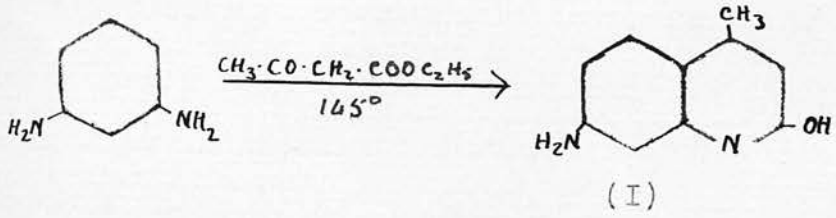
On heating this compound with β-diethylamino ethylamine in the presence of a trace of copper bronze as catalyst, condensation took place to yield 2-methyl-4-β-diethylamino-ethylamino-7:8,2':3'-pyridoquinoline. It was obtained in good yields as a crystalline derivative m.p. 115-116°, and with fuming alcoholic hydrogen bromide yielded a trihydrobromide m.p. 284°.

2-Methyl-4-(α-methyl-δ--diethylamino butyl-amino)-7:8,2':3'-pyrido quinoline was obtained in a similar manner. It proved to be a heavy brown oil which did not solidify and did not form a hydrobromide salt. With picric acid, flavianic acid and methylene disalicylic acid it formed crystalline derivatives which in the impure state quickly deteriorated to amorphous solids, which could not be recrystallised. It also formed salts with acids of lower molecular weights, such as tartaric, citric, salicylic and oxalic, but these separated as/

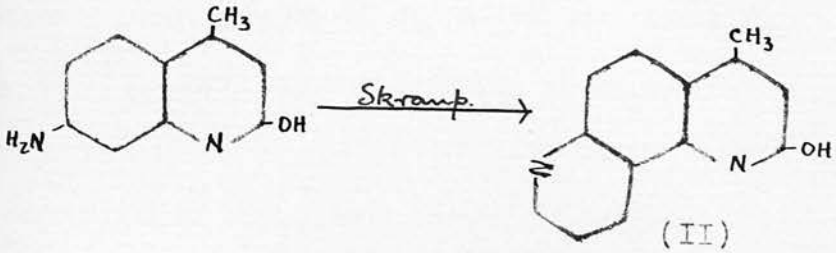
as oils which did not crystallise. It was purified to some extent by precipitating as the picrate, treating the latter with dilute caustic soda and extracting the base with ether. On reprecipitating as the picrate a more stable crystalline derivative was obtained, which analysis suggested was the tri-picrate. On heating, this salt altered in appearance about 85° and finally melted at 130°.

V. The Synthesis of 2-dialkylamino alkylamino-4-methyl-7:8,2':3'-pyrido-quinolines.

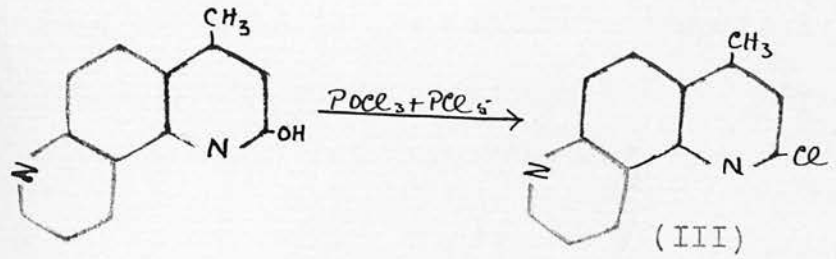
These compounds were obtained according to the following scheme of synthesis:-



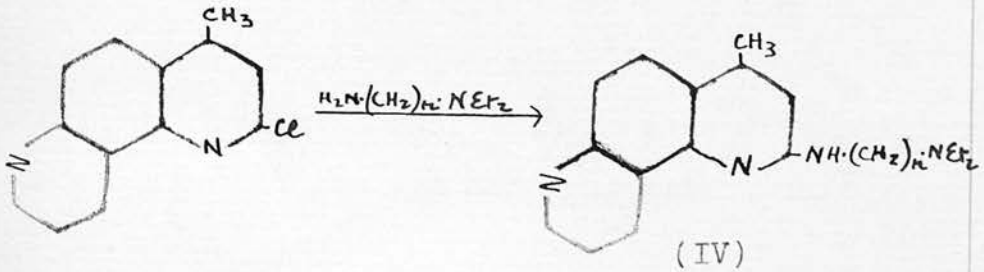
(I)



(II)



(III)



(IV)

7-Amino/

7-Amino-4-methyl-2-hydroxy quinoline (I) is described by Besthorn and Byvanck (Ber. 1896, 31, 796) who obtained it by the condensation of m-phenylenediamine with acetoacetic ester. These authors, however, were unable to prove whether it was actually the 5-amino or the 7-amino compound which they had obtained. Capps and Hamilton (J.A.C.S. 1938, 2104) converted this compound into 2-chloro-4-methyl-7-methoxy quinoline, which had already been prepared by Späth and Brunner (Ber. 57, 1243, 1924) by condensing m-anisidine with acetoacetic ester to yield 2-hydroxy-4-methyl-7-methoxy quinoline, and treating the latter with phosphorus oxychloride and phosphorus pentachloride. Capps and Hamilton showed that the compounds obtained by these two methods were identical, thus proving that the condensation product of Besthorn and Byvanck was 7-amino-4-methyl-2-hydroxy-quinoline.

When a similar condensation was carried out using m-phenylenediamine and oxalo acetic ester (cf. Section VI), ring closure took place to yield ethyl-7-amino-2-hydroxy quinoline-4-carboxylate. On hydrolysis and decarboxylation this product/

product yielded a compound which was identical with that obtained by the reduction of 7-nitro-2-hydroxy quinoline (cf. Section VI) and was therefore 7-amino-2-hydroxy quinoline. Thus, cyclisation with oxaloacetic ester takes place in a manner analogous to that with acetoacetic ester, and it seems that in such reactions with m-phenylenediamine the formation of 7-amino-quinoline derivatives rather than the 5-amino isomers is favoured.

To effect the condensation of m-phenylene-diamine and acetoacetic ester Besthorn and Byvanck heated the reactants in a sealed tube for 5-6 hours at 130°, while Capps and Hamilton carried out the reaction by heating for 19 hours in an autoclave at 130°. Our results, however, show that the reaction proceeds just as readily under atmospheric pressure, for, when equi-molecular quantities of m-phenylenediamine and acetoacetic ester were heated under reflux on the oil bath at 145° for 7 hours, 7-amino-4-methyl-2-hydroxy quinoline was obtained in a 65% yield. Both the purity of

the reactants and the temperature at which the reaction was carried out seemed to affect the course of the reaction. Lower yields after longer heating were obtained when the starting materials were impure or if the temperature was not high enough to cause the solution to boil. It was therefore found advantageous to purify the m-phenylenediamine by vacuum distillation and to redistil the aceto-acetic ester before carrying out the condensation. When 7-amino-4-methyl-2-hydroxy quinoline was subjected to the Skraup synthesis the reaction proceeded smoothly, and the product was obtained in about 60% yield. Theoretically this product can have either the angular structure (II) or the linear structure already mentioned in Section II (p. 29), but as explained there, the possibility of the latter structure may be neglected so that this compound will be 2-hydroxy-4-methyl-7:8,2':3'-pyrido quinoline. It began to decompose with sublimation about 300° and melted completely at 318° and resembled 7-amino-4-methyl-2-hydroxy-quinoline in emitting a strong blue fluorescence in alcoholic solution.

The/

The next stage in the synthesis was the conversion of this compound into 2-chloro-4-methyl-7:8,2':3'-pyrido quinoline (III). The usual method of heating with a mixture of freshly distilled phosphorus oxychloride and anhydrous phosphorus pentachloride under reflux at 120° for 3 hours proved in this case to be ineffective as the original compound was recovered unchanged. The chloro compound however was obtained in more than 90% yield by carrying out the reaction in a sealed tube at 120° for 3 hours. It melted at 160°, and showed a blue fluorescence in alcoholic solution.

By heating this chloro compound with β-diethylamino-ethylamine in the presence of a trace of copper bronze at 150° for 6 hours, 2-β-diethylamino ethylamino-4-methyl-7:8,2':3'-pyrido-quinoline was obtained in good yields. It was separated as its dihydrobromide, m.p. 281-283°. On dissolving this salt in water and making alkaline with ammonia the free base separated as pale yellow needles. It recrystallised from petroleum ether and melted at 113-114°.

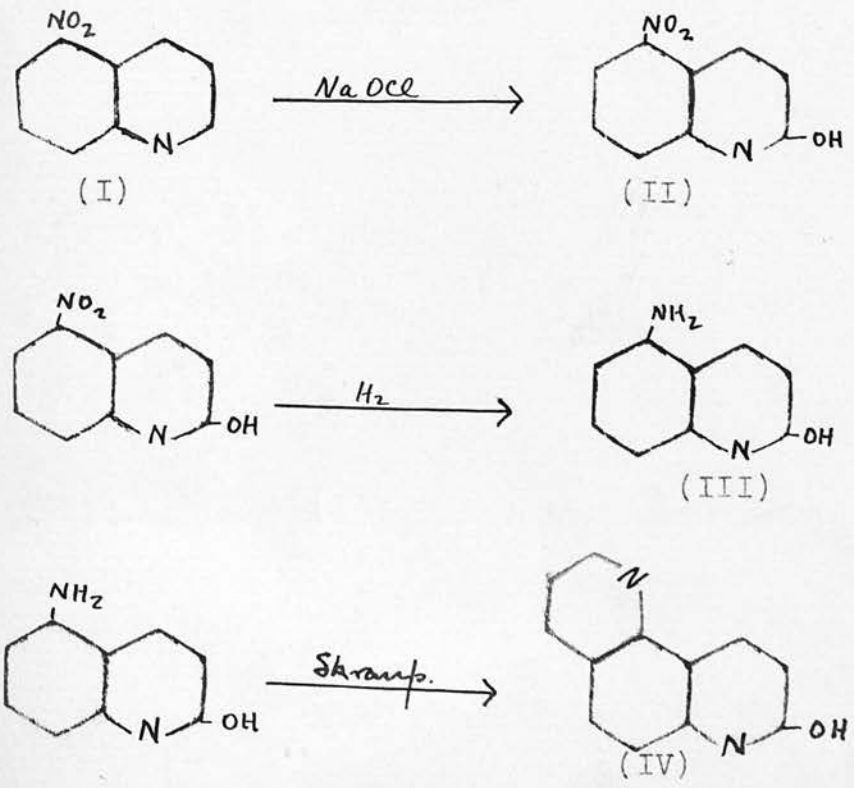
2- /

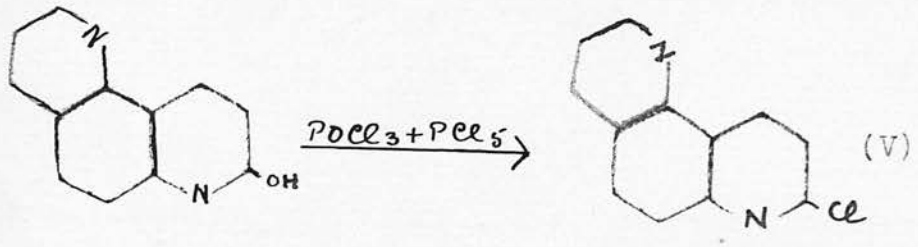
2-(α-methyl-δ-diethylamino butylamino)-4-methyl-7:8,2':3'-pyrido quinoline was obtained in a similar manner though in this case the mixture had to be refluxed at 200° for 8 hours to effect the condensation. This base proved to be a heavy brown oil which would not crystallise on standing and scratching. It gave no hydrobromide salt, but with picric acid yielded a dipicrate which re-crystallised from acetone. The pure dipicrate appeared to alter about 230° and melted at 260°C.

VI. The Synthesis of 2-Chloro-5:6,2':3'-Pyrido Quinoline and 2-Chloro-7:8,2':3'-Pyrido Quinoline.

Convenient starting materials for the synthesis of these compounds were 5-amino-2-hydroxy quinoline and 7-amino-2-hydroxy quinoline. These were prepared by the method of Capps and Hamilton (J.A.C.S. 1938, 2104) and submitted to the Skraup reaction. On treatment of the Skraup products with phosphorus oxychloride and phosphorus pentachloride there were obtained the required chloro compounds. Thus, for the preparation of 2-chloro-5:6,2':3'-pyrido quinoline the following scheme of synthesis (A) was used.

Scheme A.

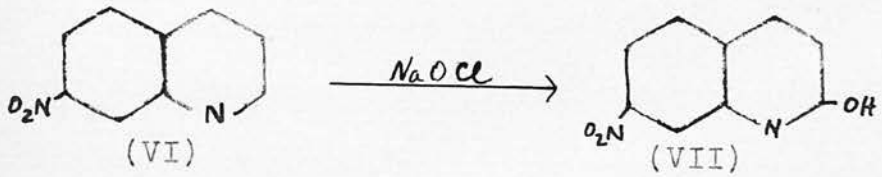




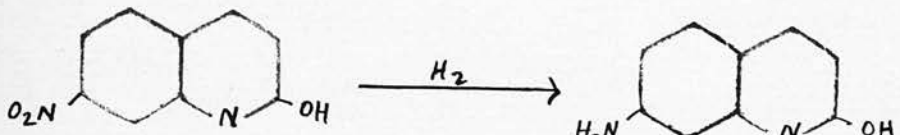
(V)

Similarly for the preparation of 2-chloro-7:8,2':3'-pyrido quinoline the scheme of synthesis (B) was followed.

Scheme B.

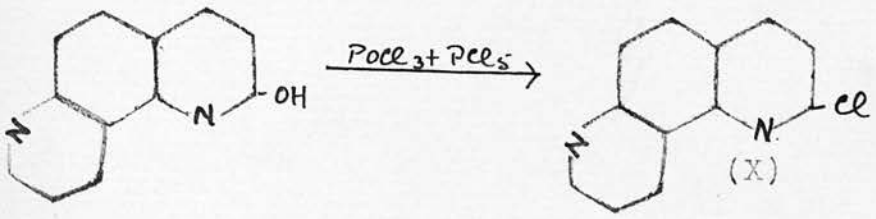


(VI) (VII)



(VIII)

(IX)

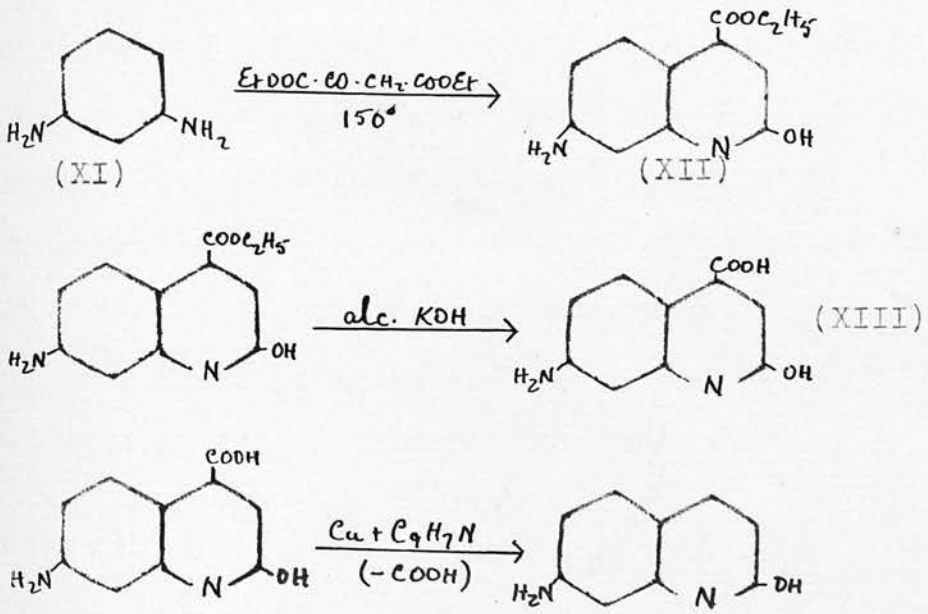


(X)

As already mentioned in a previous section (p. 2-hydroxy/

2-hydroxy-7-amino quinoline (VIII) was also prepared by an alternative method. m-Phenylenediamine and oxalo-acetic ester were condensed, in a similar way to that used in the condensation of m-phenylene-diamine and aceto acetic ester, to yield ethyl-7-amino-2-hydroxy quinoline-4-carboxylate (XII). The latter was hydrolysed to 7-amino-2-hydroxy quinoline-4-carboxylic acid (XIII) which on de-carboxylation yielded 7-amino-2-hydroxy quinoline as shown below.

Scheme C.



7-Amino-2-hydroxy quinoline prepared in this way proved/

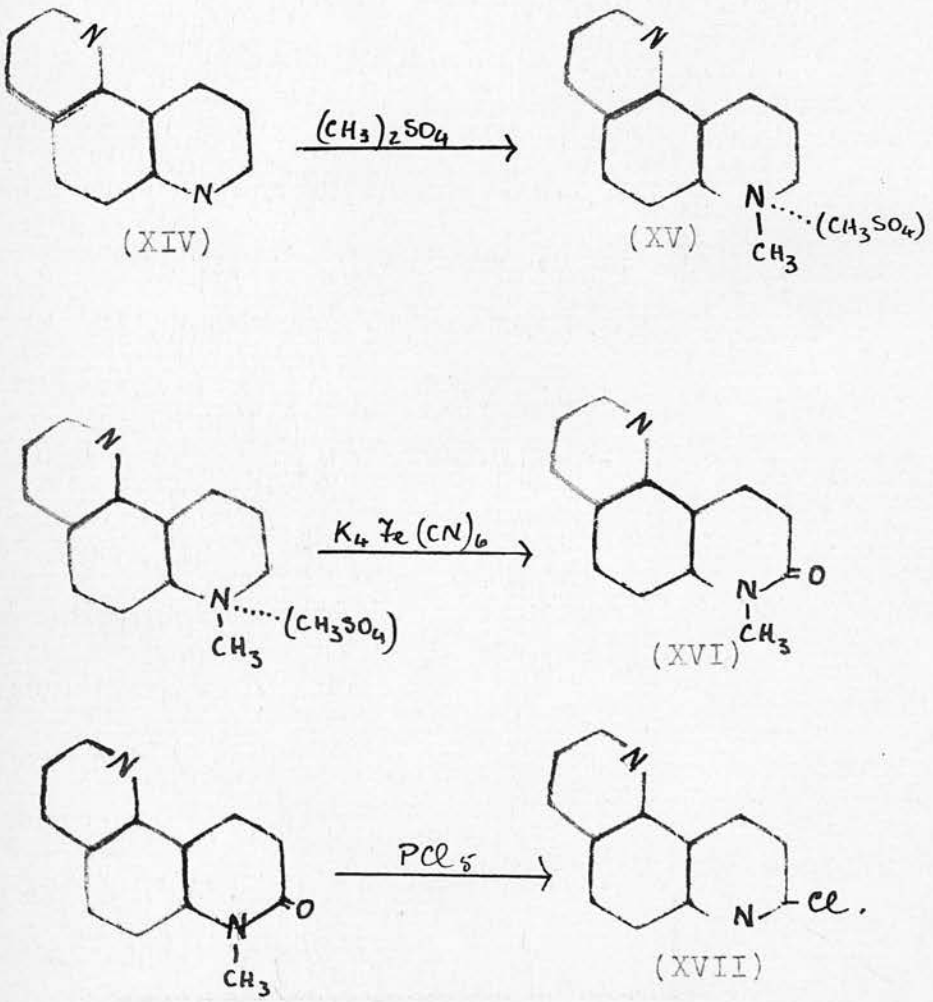
proved to be identical with the compound obtained from 7-nitro quinoline by the method of Capps and Hamilton.

2-Chloro-5:6,2':3'-pyrido quinoline melted at 145-146° while 2-chloro 7:8,2':3'-pyrido quinoline melted at 160°.

The German patent D.R.P. 654,444 (C., 1938, I, 2023) describes the preparation of a compound which is said to melt at 151° and is given the formula of 2-chloro-m-phenanthroline, (i.e. 2-chloro-5:6,2':3'-pyrido quinoline (X)). This compound was prepared according to the Scheme D given below, by condensing m-phenanthroline with dimethyl sulphate to yield N-methyl-m-phenanthrolinium methyl sulphate and oxidising the latter with potassium ferricyanide to give N-methyl-m-phenanthrolone which on treatment with phosphorus pentachloride yielded 2-chloro-m-phenanthroline.

Scheme D/

Scheme D.

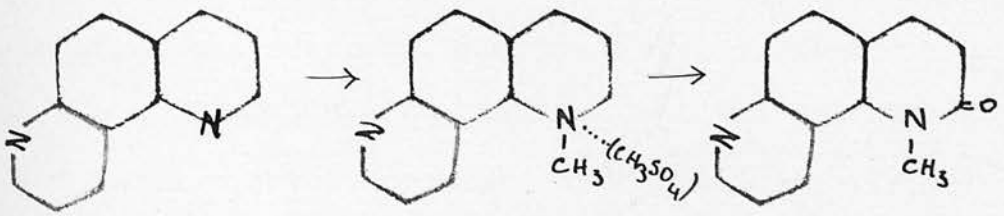


It is obvious, however, that the above series of reactions can follow two alternative routes, depending on which of the nitrogen atoms of m-phenanthroline is involved, to yield either 2-chloro-5:6,2':3'-pyrido quinoline or 2-chloro-7:8,2':3'-pyrido quinoline. Thus the first of these compounds/

compounds would result if the synthesis followed the scheme as represented above in which 5:6,2':3'-pyrido quinoline (XIV) condenses with dimethyl sulphate to yield 1-methyl 5:6,2':3' pyrido quinolinium methyl sulphate (XV) which on oxidation gives 1-methyl-2 keto-1:2-dihydro-5:6,2':3'-pyrido quinoline (XVI).

If, however, the other nitrogen atom was involved the synthesis would proceed as follows (Scheme E): 7:8,2':3'-pyrido quinoline (XVIII) ⟶ 1-methyl 7:8,2':3'-pyrido quinolinium methyl sulphate (XIX) ⟶ 1-methyl-2 keto 1:2-dihydro-7:8,2':3'-pyrido quinoline (XX) ⟶ 2-chloro-7:8,2':3'-pyrido quinoline (X).

Scheme E.



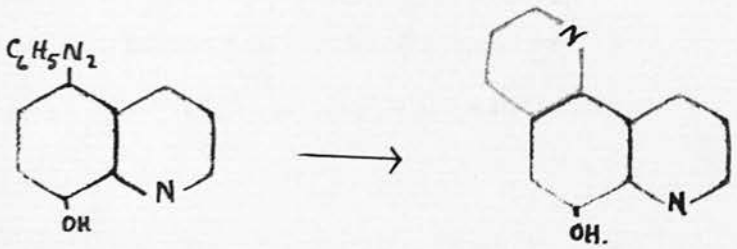
(XVIII) (XIX) (XX)

As/

As the melting point given for this chloro compound in the literature (151°) was practically midway between that of 2-chloro-5:6,2':3'-pyrido quinoline (145-146°) and 2-chloro-7:8,2':3'-pyrido quinoline (160) as prepared in our experiments, the synthesis described in the patent was repeated by us. There was thus obtained a chloro compound, m.p. 138°. When mixed with 2-chloro-5:6,2':3'-pyrido quinoline, prepared according to scheme (A), no depression of the melting point was observed. It therefore follows that the chloro compound described in the patent is 2-chloro-5:6,2':3'-pyrido quinoline and that the intermediates are 1-methyl-5:6,2':3'-pyrido quinolinium methyl sulphate (XV) and 1-methyl-2-keto-1:2-dihydro-5:6,2':3'-pyrido quinoline (XVI). This result seems to show that of the two nitrogen atoms in m-phenanthroline, the one which can be represented as being in position 1 of the quinoline nucleus in 5:6,2':3'-pyrido quinoline is that which condenses with dimethyl sulphate and is therefore presumably the more basic.

Reference might here be made to the compound described by La Coste (Ber., 16, 674, 1883) as 2-hydroxy/

hydroxy-m-phenanthroline. This compound is said to melt at 159-160° and is therefore distinct from 2-hydroxy-5:6,2':3'-pyrido quinoline obtained as above. La Coste isolated this compound as one of the products of the Skraup synthesis on m-nitraniline. He assumed that it was formed by way of 7-nitro quinoline as intermediate and that the nitro group of the latter, on being involved in the formation of a further pyridine ring, oxidised the adjacent ortho position in this new ring to give 2-hydroxy-m-phenanthroline. More recent work, however, indicates that this compound is actually 8-hydroxy-5:6,2':3'-pyrido quinoline (XXII). This was first suggested by Matsumura (J.A.C.S. 52, 3974, 1930) who obtained an hydroxy-m-phenanthroline, m.p. 157-158° by the Skraup synthesis on benzene-azo-5-hydroxy-8-quinoline.



(XXI) (XXII)

From/

From its method of preparation this compound must have the structure shown in XXII and these authors suggested that it was in fact identical with La Coste's compound. Sucharda and Mazonski (Ber., 1936, II, 2719) suggested the following mechanism to explain the formation of 8-hydroxy-5:6,2':3'-pyrido quinoline from m-nitraniline:- m-nitraniline ⟶ 5-hydroxylamino quinoline ⟶ 5-amino-8-hydroxy quinoline ⟶ 8-hydroxy-5:6,2':3'-pyrido quinoline. In support of this scheme they describe the isolation of p-amino phenol and 6- and 8-hydroxy quinolines from the Skraup synthesis using aniline, nitrobenzene, glycerine and sulphuric acid.

It thus seems that the compound obtained by La Coste is really not 2-hydroxy-5:6,2':3'-pyrido quinoline but 8-hydroxy-5:6,2':3'-pyrido quinoline, a conclusion in agreement with out observation that the true 2-hydroxy pyrido quinoline is quite different from La Coste's compound.

The 5-nitro quinoline required as starting material in the synthesis of 2-chloro-5:6,2':3'-pyrido/

pyrido quinoline was obtained by the methods already described in Section IV , and its oxidation to 5-nitro-2-hydroxy quinoline with sodium hypochlorite effected by the method of Capps and Hamilton (loc. cit.). These authors carried out the reduction of the latter compound to 5-amino-2-hydroxy quinoline using hydrogen with Raney nickel as catalyst, and claim to have obtained almost theoretical yields of the product. They do not, however, give experimental details of the reduction. In our experiments the reduction was carried out using hydrogen and Raney nickel at ordinary temperature and pressure by the method of Albert and Ritchie (J. Proc. Roy. Soc., New South Wales, 1940, 74, 74-81) which has already been mentioned above (p. 47). 5-Nitro-2-hydroxy quinoline was found to be only slightly soluble in alcohol, but with vigorous shaking of the alcoholic suspension hydrogen was absorbed in the presence of Raney nickel. The absorption was fairly slow (about 50 c.c. in 5 minutes) and as the reaction proceeded the rate of absorption decreased, so that it was necessary to warm the bottle containing/

containing the reactants to complete the reduction. 5-Amino-2-hydroxy quinoline is more soluble in alcohol than the corresponding nitro compound and as the reaction proceeded the latter was observed to gradually go into solution. On filtering off the catalyst and distilling the alcoholic solution down to dryness, about 60% yields of almost pure 5-amino-2-hydroxy quinoline were obtained.

Before the above method became available, the reduction of 5-nitro-2-hydroxy quinoline was carried out using stannous chloride and hydrochloric acid. The double salt of the base with tin chloride separated and tin was then removed as the sulphide by precipitation with hydrogen sulphide from dilute acid solution. This somewhat tedious process rendered this method, which gave a 55% yield, more laborious than the alternative one with catalytic hydrogenation.

When 5-amino-2-hydroxy quinoline was submitted to the Skraup synthesis 2-hydroxy-5:6,2': 3'-pyrido quinoline was obtained in about 60% yield. This compound began to sublime with decomposition/

decomposition about 290° and melted at 305°. On refluxing 2-hydroxy-5:6,2':3'-pyrido quinoline with a mixture of phosphorus oxychloride and phosphorus pentachloride, 2-chloro-5:6,2':3-pyrido quinoline, m.p. 145-6° was obtained in good yields.

7-Nitro quinoline was obtained by the Skraup synthesis on m-nitraniline. This method, as already mentioned (p. 45), yields a mixture of 5- and 7-nitro quinolines in the proportion of approximately 4 parts of the 5-isomer to 1 part of the 7. From this mixture 5-nitro quinoline was removed by extracting with cold petroleum ether (Kochanska and Bobranski. Ber. 69, 1809,1936) and the 7-nitro quinoline left behind recrystallised from alcohol. In this way 7-nitro quinoline was obtained in yields up to about 17% of theory.

On oxidising 7-nitro quinoline with sodium hypochlorite (Capps and Hamilton, loc. cit.), 7-nitro-2-hydroxy quinoline was obtained in good yields. The reduction of the latter was carried out in acetone in the presence of Raney nickel and hydrogen, by the method described above for 5-/

5-nitro-2-hydroxy quinoline. As with the latter, the rate of absorption of hydrogen was fairly slow and it was necessary to warm the bottle to complete the reduction. 7-Amino-2-hydroxy quinoline was thus obtained in about 50% yields.

The alternative method for the preparation of 7-amino-2-hydroxy quinoline was carried out as follows. Equimolecular quantities of redistilled m-phenylenediamine and oxaloacetic ester freshly prepared from its sodium salt, were refluxed at 145°. The reaction went more quickly and seemed more vigorous than with m-phenylenediamine and acetoacetic ester. After one hour's heating about a 35% yield of ethyl-7-amino-2-hydroxy quinoline-4-carboxylate was obtained, m.p. 262°.

On boiling with an alcoholic solution of potassium hydroxide, hydrolysis to 7-amino-2-hydroxy quinoline 4-carboxylic acid readily took place in almost quantitative yield. It was separated and purified as the potassium salt, m.p. 394° and was obtained from the latter by precipitation from an aqueous solution with a slight excess of dilute hydrochloric/

hydrochloric acid. The free acid began to decompose about 345° but did not melt below 400°.

On boiling the free acid with quinoline and copper powder the carboxylic group was removed and 7-amino-2-hydroxy quinoline was obtained in about 26% yield.

When submitted to the Skraup synthesis, 7-amino-2-hydroxy quinoline gave 2-hydroxy-7:8,2':3'-pyrido quinoline which on treatment with phosphorus oxychloride and phosphorus pentachloride in the usual manner, yielded 2-chloro-7:8,2':3'-pyrido quinoline.

For the preparation of 2-chloro-5:6,2':3'-pyrido quinoline by the method described in D.R.P. 654,444 (C. 1938, I, 2023) it was necessary to prepare m-phenanthroline. This was effected by carrying out the Skraup synthesis on m-phenylene-diamine, arsenic acid being used as oxidising agent. It was found advantageous to purify the m-phenylene-diamine by vacuum distillation before carrying out the synthesis, as less charring took place and better yields were obtained when the reactants

were/

were pure. The reaction went smoothly and after boiling 2-3 hours the mixture gave no reaction when tested for a free amino group by the diazo test. The Skraup product was precipitated with caustic soda and extracted with ether containing a small percentage of alcohol. The ethereal extract was distilled down to dryness and the m-phenanthroline so obtained purified by distillation in vacuum.

When an attempt was made to condense m-phenanthroline and dimethyl sulphate by refluxing a solution of equimolecular quantities of the reactants in methyl alcohol, a crystalline derivative, m.p. 192°, was obtained. The properties and analysis of this product showed that it was actually the m-phenanthroline salt of methyl hydrogen sulphate. The formation of this salt is evidently due to hydrolysis of the dimethyl sulphate by water present in the solution It would seem that the condensation of m-phenanthroline with dimethyl sulphate is relatively slow so that the latter compound is hydrolysed to the methyl hydrogen sulphate before it has time to/

to react with the m-phenanthroline.

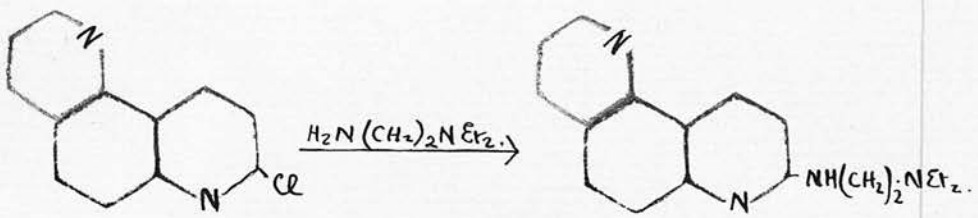
Good yields of 1-methyl-5:6,2':3'-pyrido quinolinium methyl sulphate, however, were obtained when equimolecular quantities of anhydrous dimethyl sulphate and m-phenanthroline, which had been previously dried by vacuum distillation, were heated together under reflux for one hour on the water bath. It proved to be very hygroscopic and readily absorbed moisture when exposed to the atmosphere. It was purified by recrystallising from a mixture of alcohol and acetone, and drying in vacuum over sulphuric acid. It melted at 168-169°.

When oxidised with alkaline potassium ferricyanide it gave 1-methyl-2-keto-1:2-dihydro-5:6, 2':3'-pyrido quinoline in good yield as a yellowish white crystalline derivative, m.p. 292-294°.

The final stage of the synthesis was the conversion of the latter compound into 2-chloro-5:6, 2':3'-pyrido quinoline. This was effected by heating with phosphorus pentachloride under reflux at 170-180° on the oil bath. The chloro compound was extracted with water and precipitated with sodium hydroxide. A white crystalline compound was thus obtained which was purified by one recrystallisation from dilute alcohol, m.p. 138°.

VII. The Synthesis of Dialkylamino-alkylamino-5:6, 2':3'-pyrido quinolines.

2-β-diethylamino ethylamino-5:6,2':3'-pyrido quinoline (II) was obtained by heating β-diethylamino ethylamine and 2-chloro-5:6,2':3'-pyrido quinoline, prepared as described in the previous section, in the presence of a trace of copper bronze as catalyst, at 150°. It proved to be a heavy brown oil which did not crystallise. On



(I) (II)

treatment with fuming alcoholic hydrogen bromide a crystalline hydrobromide was obtained which, however, proved to be too deliquescent to permit of further purification. The base was isolated and purified as the dipicrate, m.p. 223-4° from which it was recovered by treating with dilute sodium hydroxide solution and extracting with ether.

2/

2-(α-methyl- δ -diethylamino butylamino)-5:6,2':3'-pyrido quinoline was prepared in a similar manner by heating the chloro compound with α-methyl- δ -diethylamino butylamine at 200°. It was thus obtained as a brown oil which did not solidify. It was isolated and purified as the dipicrate, m.p. 195°.

VIII. EXPERIMENTAL.

Ethyl-β-3-acetamido phenylamino crotonate.

This compound was prepared by the method of Coffey, Thomson and Wilson (J.C.S. 1936, I, 856; see also Backeberg, J.C.S. 1935, II, 1568). m-amino acetanilide (6 g.) and acetoacetic ester (5.2 g.) together with a trace (0.05 c.c.) of hydrochloric acid were warmed on the water bath at 45° for 15 minutes. The brown solution so obtained was heated for a further 15 minutes on the boiling water bath and allowed to cool. On cooling, the clear homogeneous liquid gradually became more viscous, and on adding petroleum ether and scratching the condensation product separated as a white crystalline solid. It was filtered off and dried on a porous plate. m.p. 87-89°. Yield = 10 gms.

Further purification was effected by re-crystallising from dilute methyl alcohol from which the ethyl-β-3-acetamido-phenylamino crotonate separated as colourless needles, m.p. 92°.

5-Acetylamino-4-hydroxy-2-methyl quinoline.

Ethyl-β-3-acetamido phenylamino crotonate (10 g.) was added, in small portions at a time, to liquid paraffin previously heated to 270°. There was/

was a brisk effervescence during the addition, due to the evolution of ethyl alcohol, and a heavy brown oil separated on the bottom and sides of the flask. When cool, the paraffin was diluted with petroleum ether and filtered. A small quantity of the cyclised compound was thus obtained as a yellow crystalline product, which was washed with petroleum ether and recrystallised from boiling water, from which it separated as yellow needles. m.p. 236°. The bulk of the compound however remained in the flask in the form of a sticky brown oil adhering to the sides and bottom. This was washed with petroleum ether and extracted several times by boiling up with water and filtering off the yellow aqueous solution in the hot. On cooling 5-acetylamino-4-hydroxy-2-methyl quinoline separated from the filtrate as yellow needles. This was filtered off and purified by further recrystallisation from water. Yield = 2.5 gm. m.p. 236°. (Found C = 66.6; H = 5.8%; $C_{12}H_{12}O_2N_2$ requires C = 66.7, H = 5.6%).

This compound is soluble in alcohol and methyl alcohol, but insoluble in petroleum ether and benzene. It is soluble in cold dilute alkali, but only slightly soluble in cold dilute acid.

5/

5-Amino-4-hydroxy-2-methyl quinoline.

5-Acetylamino-4-hydroxy-2-methyl quinoline (5 g.) was boiled with 33% hydrochloric acid (100 c.c.) for 30 minutes. The brown solution so obtained was filtered hot and cooled. The filtrate was made slightly alkaline with sodium hydroxide, and a yellow crystalline compound was precipitated. It was filtered off and recrystallised from hot water from which it separated as pale yellow needles. m.p. 210°. Yield = 3.8 gm. (Found N = 16.2%; $C_{10}H_{10}ON_2$ requires N = 16.1%).

This compound gives a positive reaction when tested for a free amino group by the diazo test. It is soluble in alcohol and moderately soluble in methyl alcohol. It is soluble in dilute acid but only slightly soluble in alkali.

2-Methyl-4-hydroxy-5:6,2':3' pyrido quinoline.

5-Amino-4-hydroxy-2-methyl quinoline (4.1 g.), arsenic acid (3.4 g.), glycerine (7.05 g.) and concentrated sulphuric acid (6.4 g.) were cautiously heated on the sand bath in a flask fitted with a reflux condenser and then left to boil for 5-6 hours. The dark brown solution so obtained gave

no/

no reaction for a free amino group when tested by the diazo reaction. After cooling it was poured into cold water in which it dissolved forming a brown solution. Sodium hydroxide was then added until the solution was neutral when a light brown compound separated, which was filtered off and dried. It was conveniently purified by dissolving it in dilute hydrochloric acid and adding sodium hydroxide until just before the neutral point. Some brown tarry material separated which was filtered off, and the filtrate was neutralised with sodium hydroxide when 2-methyl-4-hydroxy-5:6,2':3'-pyrido quinoline separated. It was filtered off and dried on the water bath. Yield = 3.0 gm. m.p. 135-137°. For analysis it was purified further by recrystallisation from aqueous alcohol from which it separates as colourless needles, m.p. 142°. (Found N = 13.6%; $C_{13}H_{10}ON_2$ requires N = 13.3%).

This compound is insoluble in cold water, but is soluble to a small extent in the hot. It is slightly soluble in alcohol, methyl alcohol and benzene, but insoluble in petroleum ether. It is soluble in dilute acid and to a less extent in dilute alkali.

2/

2-Methyl-4-chloro-5:6,2':3'pyrido quinoline.

2-Methyl-4-hydroxy-5:6,2':3'-pyrido quinoline (1 g.), phosphorus pentachloride (1 g.) and phosphorus oxychloride (8 c.c.) were mixed in a small flask fitted with a narrow reflux air condenser. The mixture was heated at 120° for 3 hours on the oil bath. The excess of phosphorus oxychloride was then removed by distilling in vacuum on the water bath, and the residue extracted two or three times with hot water. The filtered aqueous solution was made alkaline with sodium hydroxide and a cream coloured compound was precipitated and was filtered off. It recrystallised from aqueous alcohol in long colourless needles, m.p. 140°. Yield = 0.8 gm. (Found C = 67.9, H = 3.6%; $C_{13}H_9N_2Cl$ requires C = 68.3, H = 3.9%). This chloro compound is soluble in petroleum ether, benzene and alcohol. It is insoluble in cold water but is soluble to a small extent in boiling water from which on cooling, it separates as colourless needles. It is soluble in dilute acid but insoluble in dilute alkali.

4 /

4-(β-diethylamino ethylamino)-2-methyl-5:6,2':3'-pyrido quinoline.

2-Methyl-4-chloro-5:6,2':3'-pyrido quinoline (0.5 g.) and β-diethylamino ethylamine (1 c.c.) together with a trace of copper bronze, were heated under reflux at 150° on the oil bath for 6 hours. After this time the dark brown solution gave a marked reaction when tested for the presence of chlorine ions. The excess β-diethylamino ethylamine was removed by vacuum distillation on the water bath. The residue was then treated with dilute sodium hydroxide solution, to remove any hydrochloric acid present, and extracted with ether. The ethereal solution was washed with water, dried over anhydrous potassium carbonate and distilled down to dryness. The base was thus obtained as a thick brown oil which did not solidify on standing and scratching. It did not give a hydrobromide on treatment with fuming alcoholic hydrogen bromide but with an alcoholic solution of picric acid it yielded a bright yellow salt. This compound recrystallised from methyl ethyl ketone, in which it is not very soluble even in the hot. m.p. 237°. The yield was almost theoretical.

Analysis/

Analysis showed it to be the dipicrate. (Found C = 48.6, H = 3.7%; $C_{19}H_{24}N_4.2.C_6H_2(OH)(NO_2)_3$ requires C = 48.6, H = 3.9%).

This dipicrate is very slightly soluble in alcohol, methyl alcohol, water and benzene. It is a little more soluble in acetone. The free base was obtained by treating the dipicrate with dilute sodium hydroxide solution and extracting with ether. Neither the base nor its hydrochloride showed fluorescence in solution.

4-(α-methyl-δ-diethylamino butylamino)-2-methyl-5:3,2':3'-pyrido quinoline.

2-Methyl-4-chloro-5:6,2':3'-pyrido quinoline (0.5 g.) and α-methyl-δ-diethylamino butylamine (1 c.c.) together with a trace of copper bronze were heated under reflux on the oil bath at 200° for 8 hours. When tested for the presence of chlorine ions the resulting dark brown solution gave a definite reaction. The excess amine was distilled off in vacuum at 150° on the oil bath. The resulting dark brown oil was then treated with dilute caustic soda solution and extracted with ether. The ethereal solution was washed with water and/

and dried over anhydrous potassium carbonate. On distilling off the ether the free base was obtained as a viscous brown oil which did not crystallise on scratching and standing. It gave no hydrobromide on treating it with fuming alcoholic hydrogen bromide, but with an alcoholic solution of picric acid yielded a dark yellow crystalline salt. This compound recrystallised from methyl ethyl ketone in which it is only moderately soluble even in the hot, as small clusters of yellowish brown crystals m.p. = 195°. Yield was almost theoretical. Subsequent analysis showed it to be the dipicrate. (Found C = 50.4, H = 4.4%; $C_{34}H_{36}O_{14}N_{10}$ requires C = 50.5%, H = 4.5%).

This dipicrate is very slightly soluble in water, alcohol, methyl alcohol and benzene. It is soluble to a small extent in hot acetone and a little more so in methyl ethyl ketone.

7-Amino-4-methyl-2-hydroxy quinoline.

(Besthorn and Byvanck, Ber. 1898, 31,798; Capps and Hamilton, J.A.C.S. 1938, 2104)

m-Phenylenediamine (27 g.), which had previously been purified by distillation in vacuum, and aceto acetic ester (32.5 g.) which had also been/

been redistilled, were heated on the sand bath in a flask fitted with a reflux air condenser at 145° for 7 hours. As the reaction proceeded, light yellow crystals began to separate, and after 7 hours the whole had set to a hard yellow coloured crystalline mass. This was washed out with methyl alcohol, and on filtering and washing thoroughly with a further quantity of methyl alcohol 7-amino-4-methyl-2-hydroxy quinoline was obtained. Further purification was unnecessary. Yield 28.5 g. m.p. = 270°. This compound showed a blue fluorescence in dilute solutions and proved to be identical with the compound described by Besthorn and Byvanck.

2-Hydroxy-4-methyl-7:8:2':3'pyrido quinoline.

7-Amino-4-methyl-2-hydroxy-quinoline (5 g.), arsenic acid (4.15 g.), glycerine (8.5 g.) and concentrated sulphuric acid (7.8 g.) were cautiously heated on the sand bath in a flask fitted with a reflux air condenser, and then left to boil for 6 hours, after which time the dark brown solution no longer gave a diazo test. The solution was then cooled and poured into twice its volume of cold water in which it dissolved to form a brown solution/

solution. This solution was filtered and on neutralising the filtrate with sodium hydroxide a light brown coloured compound was precipitated at the neutral point. It was filtered off and washed well with water.

The best method of purifying it was to dissolve it in 50% acetic acid, filter the solution and then add sodium hydroxide until the solution was moderately alkaline. In this way the base, which was precipitated at the neutral point, was redissolved in the alkali solution leaving behind some insoluble tarry material. On filtering, and neutralising the solution with dilute hydrochloric acid a pale yellow compound was precipitated, which was filtered off and washed with water. For analysis the compound was purified by recrystallisation from alcohol from which it came down in small lightly yellow coloured plates. Yield = 3.5 gm. (Found N = 13.4%; $C_{13}H_{10}ON_2$ requires N = 13.3%). It began to sublime about 300° and melted at 318° The sublimate consisted of colorless needles which proved to be 2-hydroxy-4-methyl-7:8,2':3'-pyridoquinoline/

quinoline in the pure state. Purification by sublimation, however, is not an efficient method as the bulk of the compound is decomposed in the process.

It is insoluble in water and most of the common solvents, soluble to a small extent in alcohol, and methyl alcohol. It dissolves readily in dilute acids or alkali. Its alcoholic solution possesses a strong bluish purple fluorescence, the hydrochloride salts exhibit a green fluorescence in alcohol but no fluorescence was observed with the sodium salt. Neither the base nor its salts show any fluorescence in aqueous solution.

2-Chloro-4-methyl-7:8,2':3'-pyrido-quinoline.

2-Hydroxy-4-methyl-7:8,2':3'-pyrido-quinoline (3.9 g.) was mixed with phosphorus pentachloride (3.9 g.) and phosphorus oxychloride (16 c.c.) in a Carius tube. After sealing the tube it was heated for 3 hours at 120°. On cooling the tube was opened and its contents transferred to a small flask from which the excess phosphorus oxychloride was removed by distilling in vacuum on the water bath. The residue was then extracted three or four times with warm water and the solution filtered.

The/

The filtrate was neutralised with dilute caustic soda and a pink coloured precipitate separated. This was filtered off and washed with water. The product contained chlorine. It recrystallised from alcohol or aqueous alcohol in colorless needles. m.p. 161°. Yiled = 3.4 gm. (Found C = 68.3%, H = 3.7%; $C_{13}H_9N_2Cl$ requires C = 68.3%, H = 3.9%).

This compound is soluble in dilute acids but insoluble in alkali. It is soluble in alcohol and methyl alcohol to a small extent in the cold but is more soluble in the hot. It is moderately soluble in hot petroleum ether, from which it crystallises on cooling, soluble in benzene but insoluble in acetone.

Its alcoholic solution exhibits a bluish-violet fluorescence.

2-β-diethylamino-ethylamino-4-methyl 7:8,2':3'-pyrido quinoline.

2-Chloro-4-methyl-7:8,2':3'-pyrido quinoline (0.7 g.) and β-diethylamino ethylamine (1.4 c.c.) along with a trace of copper bronze were heated together under reflux on the oil bath at 150° for 6 hours. The resulting dark brown oil gave a marked reaction when tested for chlorine ions.

The/

The excess diethyl amino ethylamine was distilled off in vacuum on the water bath and the brown oil left behind dissolved in alcohol. After filtering the alcoholic solution fuming alcoholic hydrogen bromide was added and on scratching a bright yellow crystalline compound separated. This was filtered off and purified by recrystallisation from alcohol from which it separated in long yellow needles. m.p. 281-283° (with decomposition). This proved to be the dihydrobromide of 2-β-diethylamino ethylamine. (Found C = 47.8, H = 5.5%; $C_{19}H_{24}N_4.2HBr$ requires C = 48.5, H = 5.5%). It was soluble in water and methyl alcohol, but insoluble in benzene, ligroin and acetone.

By dissolving the hydrobromide in water and adding ammonia the free base was precipitated first as an emulsion, but which on scratching yielded pale yellow needles like crystals. There were filtered off and recrystallised from petroleum ether (b.p. 60-80°) from which it separated in clusters of pale yellow needles. m.p. 113-114°. (Found C = 74.2, H = 8.3%; $C_{19}H_{24}N_4$ requires

C /

C = 74.0, H = 7.8%).

In an experiment in which the free base was isolated as such by extracting the condensation product with petroleum ether a yield of 0.7 g. was obtained.

This compound is strongly basic and readily absorbs carbon dioxide from the atmosphere. For this reason it was found necessary to take precautions against the absorption of carbon dioxide when purifying the compound for analysis.

It is very soluble in alcohol, acetone and methyl alcohol, soluble in benzene, and moderately soluble in petroleum ether. It is insoluble in water and dilute alkali but easily soluble in cold dilute acid.

2-(α-methyl-δ -diethylamino butylamino)-4-methyl-7-8,2':3'-pyrido quinoline.

2-Chloro-4-methyl-7:8,2':3'-pyrido quinoline (0.7 g.) and α-methyl-δ -diethylamino-butylamine (1.2 c.c.) together with a trace of copper bronze were heated under reflux at 200° on the oil bath for 8 hours, after which time the mixture gave a marked/

marked reaction when tested for chlorine ions. The excess amine was then removed by distilling in vacuum on the oil bath at 150-160°. The resulting dark brown oil was dissolved in alcohol and the alcoholic solution filtered. On testing a small portion of this solution with fuming alcoholic hydrogen bromide, no hydrobromide salt separated on standing or on scratching. To the alcoholic solution of the condensation product an alcoholic solution of picric acid was added and the mono-picrate immediately separated as a bright yellow crystalline compound and was filtered off. It was purified by recrystallisation from acetone in which however it is not very soluble even in the hot. It melts at 260° but begins to decompose about 230°. (Found C = 57.6, H = 5.3%; $C_{22}H_{30}N_4 . C_6H_2(OH)(NO_2)_3$ requires C = 58.0%, H = 5.7%).

The free base was obtained by treating the monopicrate with sodium hydroxide solution and extracting several times with ether. The ethereal solution was washed with water, and dried over anhydrous potassium carbonate. On distilling off the ether the free base was obtained as a light brown coloured heavy oil. Its ethereal solution exhibited a weak green fluorescence but no fluorescence was observed in dilute acid solution.

5-Nitroquinoline.

Method I: The nitration of quinoline sulphate (Claus and Setzer. J.pr. [2] 53, 390).

Quinoline sulphate was prepared by slowly adding, with vigorous stirring, concentrated sulphuric acid (50 g.) to quinoline (100 g.) contained in a beaker immersed in a good freezing mixture. The sulphate was thus obtained as a white solid mass which was powdered in a mortar and then nitrated as follows.

To a mixture of fuming sulphuric acid (10% SO_3; 300 g.) and fuming nitric acid (sp.gr. 1.50; 150 g.) cooled to -20°C., was added, with mechanical stirring, quinoline sulphate, in small portions at a time, at such a rate that the temperature never rose above -10°C.

When all the quinoline sulphate had been added, the solution which had turned reddish violet in colour, was allowed to stand for 24 hours and was then poured on to ice. A yellow solution was obtained from which there separated a yellow crystalline precipitate of the nitrate of 5-nitroquinoline. This was filtered off and washed with water. To the filtrate caustic soda was added in/

in sufficient quantity to neutralise all the sulphuric acid present, and after cooling, a further quantity of the 5-nitro quinoline was obtained as the yellow nitrate. This was filtered off and washed with water.

The nitrate, after recrystallisation from dilute nitric acid, was dissolved in hot water and the solution made alkaline with ammonia. 5-Nitroquinoline separated as an oil, which crystallised on cooling and scratching. It was filtered off, washed with water and dried in vacuum over sulphuric acid. m.p. 70-72°.

The filtrate obtained after separating the nitrate of 5-nitroquinoline was made alkaline with sodium hydroxide solution. A brown oil separated which crystallised on cooling. It was filtered off, washed well with water and recrystallised from alcohol, from which 8-nitroquinoline separated as light yellow coloured needles. It was filtered off and dried on a porous plate. m.p. 84°. Water was then added to the filtrate and a mixture of 5- and 8-nitroquinolines was precipitated. This was filtered off and dissolved in hot dilute nitric acid. On cooling a small quantity of 5-nitroquinoline/

quinoline separated as the nitrate salt, and was filtered off, washed and converted to the free base as described above. The filtrate was made alkaline with sodium hydroxide, and a further quantity of 8-nitroquinoline was obtained by repeating the process described above. Yield = 55-60 g. nitroquinoline, m.p. 70-72° (pure compound m.p. 72°) and 50-45 g. 8-nitroquinoline, m.p. 84°C (pure compound m.p. 86°C).

5-Nitroquinoline (also 7-Nitroquinoline) .

Method II. The Skranp synthesis on m-nitraniline. (Knueppel, Ber. 29, 703, 1896; Decker, J. pr. 2 63, 573; Kochanska and Bobranski, Ber. 69, 1809, 1936).

A mixture of arsenic acid (116 g.), glycerine (240 g.), m-nitroaniline (112 g.) and concentrated sulphuric acid (240 g.) was cautiously heated on the sand bath under reflux, and then left to boil for 12-13 hours. The dark brown solution thus obtained gave no reaction for a free amino group when submitted to a diazo test. On cooling, it was poured into twice its volume of cold water, left to stand overnight and filtered. The filtrate was made alkaline/

alkaline by the addition of sodium hydroxide and a dark brown resinous mass separated. This precipitate was filtered off from the cooled solution, washed well with water and dried in vacuum over sulphuric acid. The dry grey-black mass was then powdered, transferred to a flask and extracted several times by warming and shaking with ether. After six or seven such extractions an insoluble charcoal-like mass was left behind in the flask and was discarded. The ethereal solution was distilled down to dryness when there was obtained a brown oil which solidified on cooling to a light brown crystalline mass. This product consisted of a mixture of 5- and 7-nitroquinolines which were separated as follows.

The mixture was boiled up for a few minutes with petroleum ether (b.p. 60-80°), cooled and the supernatant solution decanted off. On concentrating this solution a light brown oil separated which crystallised on cooling. This white crystalline compound was filtered off and dried. It melted about 60° and consisted of 5-nitroquinoline slightly contaminated with 7-nitroquinoline. After about six such extractions the residue in the flask was boiled/

boiled up with sufficient alcohol to dissolve it in the hot and the solution was hot filtered. On cooling, crystals of 7-nitroquinoline separated and were filtered off and dried, m.p. 128°.

For purification the 5-nitroquinoline was recrystallised as the nitrate from dilute nitric acid (see Method I) and in this way there was obtained pure 5-nitroquinoline. The 7-nitroquinoline was purified by recrystallising from alcohol.
Yield = 50-60 g. 5-nitroquinoline, m.p. 72° and 15-25 g. 7-nitroquinoline, m.p. 130° (pure compound m.p. 132-3°).

5-Amino quinoline.

Method I. Reduction of 5-nitroquinoline by West's method.

5-Nitroquinoline (10 g.) was dissolved in methylated spirits (100 c.c.) containing concentrated hydrochloric acid (5 c.c.) and the mixture heated on the water bath under reflux. When the solution was boiling iron filings (10 g.) were added, in small portions at a time, and the dark red solution was then boiled for a further two hours. The solution was filtered in the hot and the residue/

residue thoroughly washed with hot methylated spirits. To the filtrate was added concentrated hydrochloric acid and, on scratching, a reddish yellow crystalline precipitate of the hydrochloride of the amine separated and was filtered off. By adding ether to the filtrate and scratching, there separated a further quantity of the hydrochloride which was filtered off and added to the original precipitate. The hydrochloride was dissolved in a small quantity of water, the solution made strongly alkaline with caustic soda and thoroughly extracted with ether. The ether extract was washed with water, dried over anhydrous sodium sulphate and distilled down to dryness. The 5-amino quinoline was thus obtained as a brown oil which readily crystallised on cooling. In this way 6-7 g. of 5-aminoquinoline was obtained which melted at between 103 and 106°. This proved to be pure enough for the purpose of condensing with ethylacetoacetate in the next stage of the synthesis, but when further purification was necessary it was effected by vacuum distillation, or with small quantities by recrystallisation from a mixture of petroleum ether and benzene.

5-Amino/

5-Aminoquinoline.

Method II. Reduction of 5-nitroquinoline by hydrogen and Raney nickel catalyst.

The reduction was carried out using the method described by Albert and Ritchie (J. Proc. Roy. Soc. N.S.Wales, 74, pp. 74-81, 1940).

(a) Preparation of the catalyst: A solution of sodium hydroxide (75 g.) in distilled water (300 c.c.) was placed in a 1 litre beaker, cooled in ice, and the finely divided nickel-aluminium alloy (75 g.) added over a period of two hours. The mixture was then heated at 110-115° for 4 hours, with occasional stirring. More sodium hydroxide was then added (100 c.c. of 20%) and heating continued until no more hydrogen was evolved (about 3 hours). After dilution to 750 c.c. the supernatant liquid was decanted and the nickel washed 6 times by decantation. It was then washed at the pump until a neutral filtrate was given. Finally it was washed 3 times with 95% alcohol and stored under alcohol.
Note: The catalyst must not be exposed to the air, and should be kept thoroughly wet during the washing operation.

(b) /

(b) Procedure: 5-Nitroquinoline (20 g.) and alcohol (200 c.c.) were placed in a rubber stoppered reagent bottle and about 10 c.c. of the black sludge of activated catalyst, prepared as above, added. The air was exhausted from the bottle, which was then connected to a graduated aspirator containing hydrogen (confined at the pressure of a few inches of water). The bottle still connected to the hydrogen aspirator, was mechanically shaken in the upright position, some 80 times a minute. Hydrogen was absorbed at the rate of about 50 c.c. per minute until 7 litres 800 c.c. had been taken up. This quantity represented the amount of hydrogen theoretically required for the reduction. Shaking was continued for another hour but only a little over 100 c.c. of hydrogen was absorbed. The flask was then uncorked, and the light yellow solution of the amine quickly filtered off from the catalyst, which was washed with alcohol and recovered for further use. The alcoholic solution was distilled down to dryness when the amine was obtained as a light brown oil which quickly solidified on cooling to a light brown crystalline mass.

Yield/

Yield = 16 g. m.p. 105-106°.

Note: It was found that if the alcoholic solution of the amine was allowed to stand exposed to the air in the presence of the catalyst, the solution turned dark brown in colour and 5-aminoquinoline was subsequently obtained in a very impure state. This is probably due to oxidation of the product in the presence of the nickel and so it is essential to filter off the catalyst immediately the bottle is disconnected from the hydrogen.

2-Methyl-4-hydroxy-7:8,2':3'pyridoquinoline.

(7-Hydroxy-9-methyl-4:10-phenanthroline. cf. Hazlewood, Hughes and Lions. J. Proc. Roy. Soc. New South Wales. (1937-38), 71, 462.)

The method used is that described by the above authors. 5-Aminoquinoline (5.6 g.) and ethyl acetoacetate (5.2 g.) were warmed together, dilute (1:1) hydrochloric acid (2 drops) added and the mixture heated at 100° for 3 hours. The oil was then washed and dried in ether, and after removal of the solvent was poured into paraffin (60 g.) preheated to 270°. There was a vigorous reaction and pale yellow plates commenced to separate almost at once. They were collected

and/

and recrystallised from boiling nitrobenzene, being practically insoluble in all the usual organic solvents. Yield = 2.3 g.

On heating, the substance was found to sublime with decomposition at 300° but did not melt completely below 390°. The white crystalline sublimate was found to be pure 2-methyl-4-hydroxy-7:8,2':3'pyridoquinoline.

2-Methyl-4-chloro-7:8,2':3'-pyridoquinoline.

2-Methyl-4-hydroxy-7:8,2':3'pyridoquinoline (1 g.), phosphorus pentachloride (1 g.) and phosphorus oxychloride (8 c.c.) were heated together in a small flask, fitted with a small bore reflux condenser, at 120° on the oil bath for 5 hours. The excess phosphorus oxychloride was then distilled off in vacuum on the water bath. The residue was extracted two or three times with hot water and the aqueous solution filtered. The filtrate was basified with ammonia and a light brown coloured compound was precipitated. This was filtered off, washed with water and purified by repeated crystallisation from alcohol. It separates as long colorless needles. m.p. 190°. Yield/

Yield = 0.85 g. (Found C = 68.0, H = 3.9%; $C_{13}H_9N_2Cl$ requires C = 68.3, H = 3.9%).

The presence of chlorine in this compound was confirmed by the usual tests. It is insoluble in cold water and very slightly soluble in the hot. It is moderately soluble in benzene and petroleum ether but insoluble in acetone. It is moderately soluble in dilute mineral acids but insoluble in caustic soda solution.

2-Methyl-4-β-diethylaminoethylamino 7:8,2':3'-pyridoquinoline.

2-Methyl-4-chloro-7:8,2':3'pyridoquinoline (1 g.) and β-diethylaminoethylamine (2 c.c.) together with a trace of copper bronze were heated, under reflux, at 150° on the oil bath. After 8 hours the brown solution gave a marked reaction when tested for free chlorine ions and heating was discontinued. The excess β-diethylaminoethylamine was then removed by distilling in vacuum on the water bath. The residue was mixed with dilute sodium hydroxide solution, to remove the hydrochloric acid, and the base extracted with ether. The ethereal solution was washed with water/

water, dried over anhydrous potassium carbonate and distilled down to dryness. The condensation product was thus obtained as a brown oil which gradually crystallised on cooling and scratching. It recrystallised from petroleum ether (b.p. 60-80°) as pale yellow plates, m.p. 115-116°. Yield = 1 gm. (Found C = 73.1, H = 8.0%; $C_{19}H_{24}N_4$ requires C = 74.0, H = 7.8%). The discrepancy in this analysis is probably due to the presence of a small amount of carbon dioxide as impurity, because the base itself was found to be strongly basic and to readily absorb carbon dioxide from the atmosphere. Thus it was found that, in an earlier analysis in which no precautions were taken against the absorption of carbon dioxide, a much lower value for the percentage of carbon was obtained. It could also be explained on the assumption that the molecule retains one quarter of a molecule of water in the crystal, but on heating in vacuum over phosphorus pentoxide at 80° for 3 hours no loss in weight was observed.

This base is very soluble in alcohol, acetone and benzene. It is insoluble in water and in dilute alkali but easily soluble in cold dilute acid/

acid.

By dissolving a small quantity of the base in alcohol and adding an equal volume of fuming alcoholic hydrogen bromide the trihydrobromide separated as slightly yellow coloured crystals. It was filtered off and dried in vacuum over sulphuric acid. It recrystallised from alcohol as colorless needles. m.p. 284-285°. (Found C = 41.8, H = 4.6%; $C_{19}H_{24}N_4.3HBr$ requires C = 41.4, H = 4.9%).

This salt is very hygroscopic and readily absorbs moisture from the atmosphere.

2-Methyl-4-(α-methyl-δ-diethylamino butylamino)-7:8,2':3'-pyridoquinoline.

2-Methyl-4-chloro-7:8,2':3'-pyridoquinoline (1 g.) and α-methyl-δ-diethylamino butylamine (2 c.c.) together with a trace of copper bronze were heated under reflux at 200° on the oil bath. After 8 hours the dark brown solution gave a marked reaction when tested for the presence of free chlorine ions. The excess amine was then distilled off in vacuum on the oil bath at 150°, and the resulting brown oil treated with dilute caustic soda solution to remove hydrochloric acid, and extracted/

extracted with ether. The ethereal solution was washed with water, dried over potassium carbonate and distilled down to dryness. There was thus obtained a heavy brown oil which did not crystallise on scratching or on standing. It did not give a hydrobromide with fuming alcoholic hydrogen bromide. A small amount was dissolved in alcohol and an alcoholic solution of picric acid added. A bright yellow compound separated, it had a crystalline appearance but on filtering and standing in the atmosphere it tended to change to an amorphous brown solid. This solid was insoluble in water and alcohol but was fairly soluble in acetone. Attempts were made to recrystallise it from a mixture of acetone and alcohol, but the compound separated as a sticky amorphous mass which would not crystallise.

With flavianic acid in alcoholic solution the base yielded a heavy yellow precipitate, but on filtering off the flavianate it tended to change to an amorphous brown mass, which was insoluble in the usual organic solvents, and could not be recrystallised. Similarly, with methylene/

methylene disalicylic acid a white precipitate was obtained which deteriorated to a brown amorphous mass, and was too insoluble in most organic solvents to permit of purification by recrystallisation. Further attempts to isolate a tractable crystalline derivative of the base with compounds such as salicylic acid, citric acid, tartaric acid and oxalic acid were unsuccessful because the salts separated as heavy oils which would not crystallise.

Some measure of purification, however, was effected by precipitating the base as the picrate, treating the latter with dilute caustic soda solution and extracting the base with ether. On washing the ethereal solution with water, drying it over potassium carbonate and distilling down to dryness, the base was again obtained as a brown oil. On reprecipitating as the picrate a more stable compound was obtained which retained its yellow crystalline appearance after filtering and standing in the atmosphere. Attempts to recrystallise this picrate however were again unsuccessful. An analysis on the compound thus obtained suggests it is the tri-picrate. (Found

C/

C = 46.9, H = 3.3%; $C_{22}H_{30}N_4.3.C_6H_2(OH)(NO_2)_3$ requires C = 46.3, H = 3.9%).

On heating this tripicrate it changes in appearance about 85° and finally melts completely about 130°.

5.Nitro-2-hydroxy quinoline.

(Capps and Hamilton, J.A.C.S. 1938, p.2104; Claus and Setzer, J. pr. [2], 53, 390).

5-Nitroquinoline (10 g.) was dissolved in water (50 c.c.) by the addition of sulphuric acid and was poured into 2 litres of water at 60°C. Sodium hydroxide solution was then added until the acidity was such that the nitro compound just remained insolution. (This was found to be at a pH of 2.5; if the solution was more acid it was found that on adding the hypochlorite, decomposition occurred with the evolution of chlorine, and if more alkaline the base tended to separate and did not react properly). A solution of sodium hypochlorite (5%) was run in until a solid began to appear. After standing overnight, this solid was filtered off and dissolved in 10% caustic soda solution. On acidifying a light yellow precipitate of 5-nitro-2-hydroxy quinoline separated, and was filtered/

filtered off and dried on the water bath. Yield = 80-85% of theory. The product melted at 295° and was recrystallised from alcohol when it was obtained in the pure state, m.p. 304°.

5-Amino-2-hydroxy quinoline.

Method I: Reduction of 5-nitro-2-hydroxy quinoline with stannous chloride and hydrochloric acid.

Stannous chloride (45 g.) was dissolved in concentrated hydrochloric acid (110 c.c.) and the solution heated on water bath under reflux. To the boiling solution, 5-nitro-2-hydroxy quinoline (11 g.) was added in small portions at a time. There was a vigorous effervescence on each addition and the solution turned dark brown in colour. When all the nitro compound had been added the solution was boiled for a further 6 hours. On cooling a yellow crystalline precipitate separated and was filtered off. It was dissolved in water and the hot solution saturated with hydrogen sulphide. Tin sulphide separated and was filtered off and washed well with boiling water. Hydrogen sulphide was then passed into the hot solution again and the process repeated until all the tin had been removed from the solution.

On/

On concentrating the solution down to small volume the hydrochloride of the base separated as pale yellow crystals, which were filtered off and dissolved in the minimum quantity of hot water. Ammonia was added until the solution was slightly alkaline when 5-amino-2-hydroxy quinoline separated as a white crystalline precipitate which was filtered off and dried on the water bath. Yield = 5 g. m.p. 240°. The pure compound, m.p. 250° was obtained by recrystallisation from alcohol.

5-Amino-2-hydroxy quinoline.

Method II. Reduction of 5-nitro-2-hydroxy quinoline with hydrogen and Raney nickel.

The nickel catalyst was prepared, and the reduction carried out by the method described by Albert and Ritchie (J. Proc. Roy. Soc. New South Wales, 1940, 74, 74-81; see also above - 5-amino-quinoline, Method II.)

5-Nitro-2-hydroxy quinoline (10 g.) and alcohol (100 c.c.) were placed in a rubber stoppered reagent bottle and the catalyst added (about 10 c.c. of the black sludge of the activated catalyst in alcohol). The bottle was exhausted and connected to a graduated aspirator containing hydrogen (confined at the/

the pressure of a few inches of water). It was then mechanically shaken, in the upright position, some 80 times a minute. Hydrogen was absorbed at the rate of about 50 c.c. in 5 minutes until just over 3 litres had been taken up. The bottle was then warmed in hot water for a few minutes and shaking continued for a further 2 hours, when another litre of hydrogen was absorbed. Theoretically, the reduction of 10 g. of 5-nitro-2-hydroxy quinoline requires 3.8 litres of hydrogen. Shaking was discontinued after this time and it was observed that all the compound had gone into solution in the alcohol. This alcoholic solution was filtered off from the catalyst which was found to be still active and after washing with alcohol was recovered for further use. On distilling the solution down to dryness 5-amino-2-hydroxy-quinoline was obtained. m.p. 245°.

2-Hydroxy-5:6,2':3'-pyrido quinoline.

5-Amino-2-hydroxy quinoline (4.0 g.), arsenic acid (3.5 g.), glycerine (7.2 g.) and sulphuric acid (6.6 g.) were cautiously heated on the sand bath in a small flask fitted with a reflux condenser. The/

The mixture was boiled gently for 3 hours, after which time it no longer gave a reaction when tested for a free amino group by the diazo test. It was allowed to cool and was poured into water in which it dissolved to form a brown solution. This solution was filtered and neutralised with caustic soda when a light brown compound separated. This was filtered off and dried on the water bath. It was best purified by dissolving in dilute acid solution and adding dilute sodium hydroxide solution until just before the neutral point. In this way the base was retained in solution but some black tarry material was precipitated and was filtered off. By neutralising the filtrate the base was obtained in a moderately pure state and was filtered off and dried. Yield = 3 g. This compound, on heating, began to sublime with decomposition between 280 and 290° and melted at 305°. The white crystalline sublimate consisted of pure 2-hydroxy-5:6,2':3'-pyrido quinoline. For analysis a sample of the compound was purified by sublimation and re-crystallisation from alcohol from which it separates in colourless needles. (Found C = 72.9, H = 4.3%, $C_{12}H_8ON_2$ requires C = 73.4, H = 4.1%). It melted

at/

at 315° with previous decomposition and sublimation at 290°. This base is insoluble in water, and is only slightly soluble in most organic solvents. It is soluble in dilute acid and alkali.

2-Chloro-5:6,2':3'-pyrido quinoline.

2-Hydroxy 5:6,2':3'-pyrido quinoline (1 g.), phosphorus pentachloride (1 g.) and phosphorus oxychloride (8 c.c.) were heated together on the oil bath at 120° for 3 hours, in a flask fitted with a narrow reflux air condenser. The excess oxychloride was removed by distilling in vacuum on the water bath. The residue was extracted 2 or 3 times with hot water, and the extracts filtered. The filtrate was made alkaline with sodium hydroxide and a pink coloured precipitate separated. This was filtered off and dried. It was found to contain chlorine. It recrystallised from alcohol in colorless needles. m.p. 145-146°. Yiled = 0.85 g. (Found C = 66.8, H = 3.3. $C_{12}H_7N_2Cl$ requires C = 67.1, H = 3.3%).

This compound is very slightly soluble in water, soluble in alcohol, moderately soluble in methyl alcohol and insoluble in petroleum ether.

It/

It is soluble in dilute mineral acids but insoluble in alkali.

2-β-diethylamino-ethylamino-5:6,2':3'-pyrido quinoline.

2-Chloro-5:6,2':3'-pyrido quinoline (0.5 g.) and β-diethylamino ethylamine (1 c.c.) together with a trace of copper bronze were heated under reflux at 150° on the oil bath. After 5 hours the solution gave a marked reaction when tested for the presence of free chlorine ions. After distilling off the excess β-diethylamino-ethylamine, the resulting brown oil was treated with dilute sodium hydroxide solution, to remove hydrochloric acid, and the free base extracted with ether. The ethereal solution was washed with water, dried over potassium carbonate and distilled down to dryness. The brown oil thus obtained did not solidify on standing and scratching. A small portion in alcoholic solution was treated with fuming alcoholic hydrogen bromide and a crystalline hydrobromide separated on scratching. It was filtered off, but readily absorbed moisture from the air and quickly deteriorated to a sticky mass. It proved to be

too/

too deliquescent to serve as a suitable salt for isolating and purifying the base. The base was then dissolved in alcohol and an alcoholic solution of picric acid added. The dipicrate immediately separated as a bright yellow crystalline precipitate. It recrystallised from methyl ethyl ketone as small rectangular yellow plates. m.p. 223-224°. (Found C = 47.9, H = 3.8%; $C_{18}H_{22}N_4.2C_6H_2(OH)(NO_2)_3$ requires C = 47.9, H = 3.7%).

This dipicrate is very slightly soluble in water, benzene, alcohol and methyl alcohol. It is a little more soluble in acetone from which it crystallises in small quantities.

By treating the dipicrate with dilute caustic soda solution, extracting with ether and distilling down the dried ether solution to dryness, 2-β-diethylamino ethylamino-5:6,2':3'-pyrido quinoline is recovered as a light brown oil. It shows a green fluorescence in ethereal solution but in dilute hydrochloric acid no fluorescence was observed.

2-/

2-(α-methyl-δ-diethylamino-butylamino)-5:6,2':3'-pyrido quinoline.

2-Chloro-5:6,2':3'-pyrido quinoline (0.8 g.) and α-methyl-δ-diethylamino butylamine (1.6 c.c.) along with a trace of copper bronze, were heated under reflux at 200° on the oil bath. After 8 hours the brown solution gave a marked reaction when tested for the presence of chlorine ions. The excess amine was removed by distilling in vacuum at 150° on the oil bath and the resulting brown oil treated with dilute caustic soda solution and extracted with ether. The ethereal solution was washed with water, dried over potassium carbonate and distilled down to dryness. The base was thus obtained as a brown oil which did not solidify on standing and scratching. A small portion in alcoholic solution was treated with fuming alcoholic hydrogen bromide, but no hydrobromide separated. The base was then dissolved in alcohol and an alcoholic solution of picric acid added. The dipicrate separated as an oil, but on scratching, it readily crystallised and was filtered off. It recrystallised from methyl ethyl ketone as small yellow prisms. m.p. 195°. Yield = 1.6 g.

(Found/

(Found C = 50.0, H = 4.1%; $C_{21}H_{28}N_4.2C_6H_2(OH)(NO_2)_3$ requires C = 49.9, H = 4.3%).

The dipicrate is slightly soluble in alcohol, methyl alcohol, benzene and water, and a little more soluble in acetone. From it the pure base was obtained by treating with dilute sodium hydroxide solution, extracting with ether and distilling the ethereal solution down to dryness. The base proved to be a light brown oil which showed a weak green fluorescence in ethereal solution but showed no fluorescence in dilute hydrochloric acid solution.

Ethyl-7-amino-2-hydroxy-quinoline-4-carboxylate.

m-Phenylenediamine (10.8 g.), which had been previously purified by vacuum distillation, and oxalo-acetic ester (18.8 g.) freshly prepared from the sodium salt, were heated together under reflux at 145° on the oil bath. The reaction went very readily and crystals soon began to separate. After one hour the condensation product was obtained as a bulky crystalline mass, which was washed out of the flask with methyl alcohol, filtered and again washed with methyl alcohol. It recrystallised from/

from alcohol as long yellow glistening needles, m.p. 262°. Yield = 8 g. (Found C = 61.8, H = 4.9% ; $C_{12}H_{12}O_3N_2$ requires C = 62.1, H = 5.2%). This compound is slightly soluble in the cold in water and methyl alcohol but is more soluble in the hot. It is slightly soluble in benzene and petroleum ether. It dissolves in hot dilute sodium hydroxide solution to give a colourless solution and in dilute acid to give a yellow solution.

7-Amino-2-hydroxy quinoline-4-carboxylic acid.

Ethyl 7-amino-2-hydroxy quinoline-4-carboxylate was boiled with an alcoholic solution of potassium hydroxide (60 c.c. of 5%) for 20 minutes under reflux. The potassium salt of the free acid separated as light brown crystals and was filtered off. A further quantity of the potassium salt was obtained from the filtrate by adding acetone. It recrystallised from aqueous acetone as long colourless needles. m.p. 394° (with decomposition). The yield was almost theoretical.

This salt is readily soluble in cold water.

From/

From the aqueous solution the free acid is precipitated by the addition of dilute mineral acid but redissolves in excess. It is slightly soluble in hot alcohol and more soluble in methyl alcohol. It showed a blue fluorescence in alcohol and a green fluorescence in water.

The free acid was obtained by dissolving the recrystallised potassium salt in water and precipitating with a small quantity of hydrochloric acid, excess being avoided. For analysis a small quantity was recrystallised from alcohol in which it is only slightly soluble even in the hot. (Found C = 58.5, H = 3.8%; $C_{10}H_8O_5N_2$ requires C = 58.8, H = 3.9%).

This compound proved to be almost insoluble in the usual organic solvents. On heating it began to decompose about 345° but did not melt below 400°. Its alcoholic solution exhibited a strong green fluorescence. No fluorescence was observed in hydrochloric acid solution.

7-Amino-2-hydroxy quinoline.

7-Amino-2-hydroxy quinoline 4-carboxylic acid (2 g.), finely divided copper powder (1 g.) and quinoline/

quinoline (20 c.c.) were boiled gently under reflux for 3 hours, and the solution filtered in the hot. Water was added to the filtrate and the quinoline removed by steam distillation. The aqueous solution thus obtained was concentrated to small volume, filtered and cooled. 7-Amino-2-hydroxy-quinoline separated as light brown crystals and was filtered off and recrystallised from water. It separated as white needles, m.p. 292-293°. Yield= 0.5 g. When mixed with a sample of 7-amino-2-hydroxy quinoline prepared by reducing 7-nitro-2-hydroxy quinoline, as described below, there was no depression of the melting point.

7-Nitro quinoline.

This compound was obtained by carrying out the Skraup synthesis on m-nitraniline as described above (see 5-Nitro quinoline Method II, p. 96).

7-Nitro-2-hydroxy-quinoline.

7-Nitroquinoline was oxidised with sodium hypochlorite by the method of Capps and Hamilton, already described above in connection with the preparation of 5-nitro-2-hydroxy quinoline (see p.109). 7-Nitro-2-hydroxy quinoline was thus obtained in about/

about 75% yield. The crude product melted at 318-320°. For identification purposes a sample was purified further by recrystallisation from alcohol, in which, however, it is not very soluble even in the hot. It separated as pale yellow needles, m.p. 340°.

7-Amino-2-hydroxy quinoline.

Method II. Reduction of 7-nitro-2-hydroxy quinoline.

The reduction was carried out in acetone solution using hydrogen and Raney nickel, by the method already described for the reduction of 5-nitro-2-hydroxy quinoline (see above 5-Amino-2-hydroxy quinoline, Method II, p.111). 7-Amino-2-hydroxy quinoline was thus obtained in about 50% yields. It was purified by recrystallisation from aqueous alcohol from which it separated as colourless needles, m.p. 292°.

2-Hydroxy-7:8,2':3'-pyrido quinoline.

7-Amino-2-hydroxy quinoline (1 g.), arsenic acid (0.8 g.), glycerine (1.8 g.) and sulphuric acid (1.6 g.) were cautiously heated on the sand bath in a small flask fitted with a reflux condenser and the mixture boiled gently for 3 hours. After/

After this time the dark brown solution gave no reaction when tested for a free amino group by the diazo test. It was allowed to cool and was poured into water in which it dissolved to form a brown solution. The solution was then filtered and the filtrate neutralised with sodium carbonate solution, when a light brown compound was precipitated. It was filtered off and recrystallised from alcohol from which it separated as pale yellow needles. Yield = 0.5 g. After recrystallising three times from alcohol, it shrank about 275°, with sublimation, and melted completely at 290°. Analysis, however, showed that it was still not pure.

This compound is insoluble in water, benzene and petroleum ether, slightly soluble in hot methyl alcohol and more soluble in hot absolute alcohol. It is soluble in dilute mineral acid and in dilute sodium hydroxide solution.

2-Chloro-7:8,2':3'-pyrido quinoline.

2-Hydroxy-7:8,2':3'-pyrido quinoline (0.5 g.), phosphorus pentachloride (0.5 g.) and phosphorus oxychloride (4 c.c.) were heated together under reflux, on the oil bath at 120°, for 3 hours. The excess/

excess phosphorus oxychloride was then removed by distilling in vacuum on the water bath, and the residue extracted with hot water. The aqueous solution was filtered and basified with sodium hydroxide solution. A light brown precipitate separated and was filtered off and recrystallised from dilute alcohol. It separated as small colourless needles, m.p. 160°. Yield = 0.35 g. (Found, C = 66,6; H = 3.1%; $C_{12}H_7N_2Cl$ requires C = 67.1, H = 3.3%).

This compound is very slightly soluble in water, soluble in alcohol, and insoluble in petroleum ether. It is soluble in dilute mineral acids but insoluble in sodium hydroxide solution.

m-Phenanthroline.

m-Phenylenediamine (21.6 g.) previously purified by vacuum distillation, arsenic acid (58 g.), glycerine (120 g.) and concentrated sulphuric acid (120 g.) were cautiously mixed, then heated on the sand bath so that the mixture was kept gently boiling. After 2½ hours it gave no reaction for a free amino group when tested by the diazo test. It was/

was allowed to cool and poured into water in which it formed a dark brown solution with a green fluorescence. After filtering, the solution was made strongly alkaline with sodium hydroxide solution, cooled and extracted several times with ether which contained a small percentage of alcohol. The ethereal extract, which showed a green fluorescence, was dried over sodium sulphate and the ether distilled off. There was thus obtained a dark brown oil which readily solidified on cooling and scratching. This product was twice distilled in vacuum when 10.9 g. of anhydrous m-phenanthroline was obtained.

m-Phenanthrolinium methyl sulphate.

m-Phenanthroline (0.9 g.) and dimethyl sulphate (0.46 c.c.) were refluxed in methyl alcohol (15-20 c.c.) for one hour and the methyl alcohol subsequently removed by distillation. A reddish yellow crystalline solid mass was obtained which readily recrystallised from methyl alcohol as pale yellow rectangular prisms, m.p. 192°.

When an aqueous solution of this compound was basified with sodium hydroxide solution, an oil/

oil was obtained which crystallised on scratching and proved to be unchanged m-phenanthroline. The compound therefore appears to be a simple salt of m-phenanthroline and analysis confirmed that it was m-phenanthrolinium methyl sulphate. (Found: C = 53.4, H = 3.7%; $C_{12}H_8N_2.MeHSO_4$ requires C = 53.8, H = 4.1%).

This compound is easily soluble in water and is fairly hygroscopic. It is not very soluble in cold methyl alcohol or ethyl alcohol but is readily soluble in the hot. It is insoluble in benzene and in petroleum ether.

2-Chloro-5:6,2':3'-pyrido quinoline.

Method II. (D.R.P. 654,444. C. 1938, I, 2023)

To m-phenanthroline (3.6 g.), which had been previously dried by vacuum distillation, was added dimethyl sulphate (1.84 c.c.) which had been dried over anhydrous potassium carbonate. The mixture became quite hot and was heated on the water bath for one hour, under reflux. To the reddish brown liquid so obtained acetone was added and on scratching, the oil changed to a sticky solid which became/

became crystalline on repeatedly washing with acetone. This material was very hygroscopic and was dried in a vacuum dessicator over sulphuric acid when it melted indefinitely at 145°. When a concentrated solution in alcohol was cooled the crystals which first separated melted in the neighbourhood of 130°. Part of the alcohol was removed from the mother liquor, acetone added in the hot and on cooling a further crop of crystals was obtained which melted at 162-164°. This material when again recrystallised melted at 168-169° and was evidently identical with the methyl-pyrido quinolinium methyl sulphate, mentioned in the patent, melting at 171°.

It is probable that the crude product is contaminated with a small amount of the methyl hydrogen sulphate produced by hydrolysis of the dimethyl sulphate by a small quantity of water which it is difficult to exclude without special precautions. It is known that m-phenanthroline very readily forms a hydrate in which presumably one of the nitrogen atoms is involved and it is possible that the molecule of water being in contact with the nitrogen atom may account for the ease with

which/

which dimethyl sulphate is hydrolysed when an attempt is made to condense it with m-phenanthroline (see previous experiment).

Slightly impure 1-methyl-5:6,2':3'-pyrido quinolinium methyl sulphate (m.p. 164°) was oxidised as follows. Potassium ferricyanide (3 g.) was dissolved in a small quantity (10 c.c.) of water and to it were added alternately, drop by drop, an aqueous solution of the methyl sulphate (1 g.) and a solution of potassium hydroxide (0.7 g.). The mixture was allowed to stand for an hour and a light yellow crystalline precipitate of 1-methyl-2-keto-1:2-dihydro-5:6,2':3'-pyrido quinoline separated. It was filtered off and dried on the water bath. m.p. 292-294°. Yield = 0.5 g. (D.R.P. 654,444 gives m.p. 195°).

1-Methyl-2-keto-1:2-dihydro-5:6,2':3'-pyrido quinoline (0.5 g.) was mixed with phosphorus pentachloride (1 g.) and the mixture heated under reflux for 5 hours on the oil bath at 170-180°. When cool the product was extracted twice with warm water. The aqueous solution was filtered and made slightly alkaline by the addition of sodium hydroxide. A white crystalline precipitate separated/

separated and was filtered off and dried on the water bath. In this crude state it melted at 130° but on recrystallising once from alcohol melted at 138°. The yield was very poor as the bulk of the material remained behind on extraction with water, and there was not enough available for further purification. When mixed with a sample of 2-chloro-5:6,2':3'-pyrido quinoline (m.p. 145-6°) prepared from the corresponding 2-hydroxy-5:6,2':3'-pyrido quinoline as described above, the melting point was 138-142°. When mixed with 2-chloro-7:8,2':3'-pyrido quinoline (m.p. 160°) it melted at 119-125°.

There is therefore little doubt that the product is in fact 2-chloro-5:6,2':3'-pyrido quinoline.

IX. SUMMARY.

S U M M A R Y.

I. A survey of the literature dealing with antimalarial compounds is given, with special reference to the relationship between chemo-therapeutic activity and chemical constitution.

II. The relation between various isomeric derivatives of m-phenanthroline is discussed and the constitution of certain new compounds and of others of hitherto doubtful orientation has been established.

III. The condensation of m-amino acetanilide with ethyl aceto acetate has been carried out and the product cyclised by the method of Conrad and Limpach. It has been shown that the compound so obtained is 5-acetylamino-4-hydroxy-2-methyl quinoline and not the isomeric 7-acetylamino derivative.

IV. /

IV. The following chloro derivatives of m-phenanthroline have been prepared: 2-methyl-4-chloro-5:6,2':3'-pyrido quinoline; 2-methyl-4-chloro7:8,2':3'-pyrido quinoline; 2-chloro-4-methyl-7:8,2!3'-pyrido quinoline; 2-chloro-5:6,2':3'-pyrido quinoline and 2-chloro-7:8,2':3'-pyrido quinoline.

It is shown that the chloro m-phenanthroline described in D.R.P. 654,444 (C. 1938, I, 2023) and assumed to be 2-chloro-5:6,2':3'-pyrido quinoline does in fact have this structure, and is not the isomeric 2-chloro-7:8,2':3'-pyrido quinoline.

V. The first four of the above chloro compounds were condensed with the appropriate bases to yield respectively: 4-(β-diethylamino ethylamino)-2-methyl-5:6,2':3'-pyrido quinoline and 4-(α-methyl-δ-diethylamino butyl amino)-2-methyl-5:6,2':3'-pyrido quinoline; 4-(β-diethylamino ethyl amino)-2-methyl-7:8,2':3'-pyrido quinoline and 4-(α-methyl/

methyl- δ -diethylamino-butyl amino)-7:8,2':3'-pyrido quinoline; 2-(β-diethylamino ethyl amino)-4-methyl-7:8,2':3'-pyrido quinoline and 2-(α-methyl- δ -diethylamino-butyl amino)-7:8,2':3'-pyrido quinoline; 2-(β-diethylamino ethyl amino)-5:6,2':3'-pyrido quinoline and 2-(α-methyl- δ -diethylamino-butyl amino)-5:6,2':3'-pyrido quinoline.